THE DETERMINATION OF INCIDENCE AND RISK FACTORS FOR DEEP VENOUS THROMBOSIS IN THE MEDICAL INTENSIVE CARE UNIT

A dissertation submitted in partial fulfillment of the rules and regulations for the MD Branch – I General Medicine Degree Examination of the Tamil Nadu Dr. M.G.R. Medical University, Chennai, to be held in April 2015.

DECLARATION CERTIFICATE

This is to declare that the dissertation titled "The Determination of Incidence and Risk Factors for Deep Venous Thrombosis in the Medical Intensive Care Unit" is my own work, done under the guidance of Dr.Thambu David, Professor and Head, Department of Medicine II, submitted in partial fulfillment of the rules and regulations for the MD Branch I – General Medicine Degree Examination of the Tamil Nadu Dr. M.G.R. Medical University, Chennai, to be held in April 2015.

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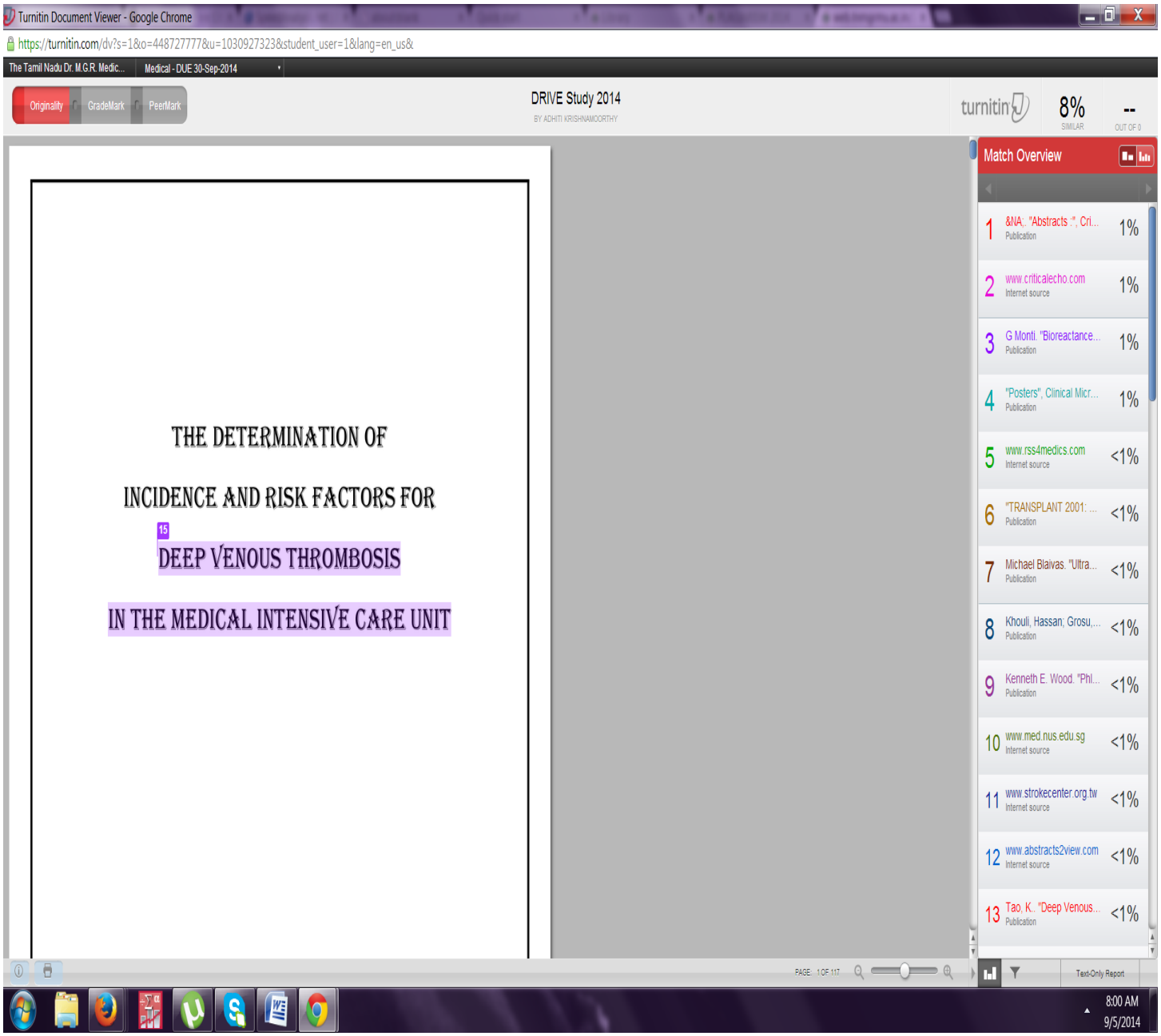
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Dr. Adhiti.K, PG Registrar, General Medicine, Dr. Thambu David, Medicine-II, Dr. Samuel George Hansdak, Medicine-IV, Dr. John Victor Peter, Dr. Kishore Kumar Pichamuthu, MICU, Dr. Sudha Jasmine, Medicine-II, Dr. Thomas Isaiah Sudarsan, MICU, Dr. Sridhar Gibikote.V, Radiodiagnosis, Dr. L. Jeyaseelan, Biostatistics

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Could you please sign the agreement and send it to Dr. Nihal Thomas, Addl. Vice Principal (Research), so that the grant money can be released.

With best wishes,

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CC: Dr. Thambu David, Department of Medicine-II

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TITLE OF THE ABSTRACT: The Determination of Incidence and Risk Factors for Deep Venous Thrombosis in the Medical Intensive Care Unit

DEPARTMENT: General Medicine

NAME OF THE CANDIDATE: Adhiti.K.

DEGREE AND SUBJECT: MD, General Medicine

NAME OF THE GUIDE: Dr. Thambu David, Professor and Head, Medicine – II, Christian Medical College, Vellore.

OBJECTIVES: This study was aimed at determining the incidence of deep venous thrombosis (DVT) in the medical intensive care unit (while on thromboprophylaxis), and describing the risk factors associated with the same.

METHODS: All patients getting admitted to the medical intensive care unit (MICU) underwent screening with compression ultrasound, at four points on each side (jugular, axillary, femoral and popliteal), after informed consent. This was done on days 1, 3 and 7 of admission into the MICU. All patients were on thromboprophylaxis (pharmacological/mechanical) as per the existing protocol. The primary outcome was the incidence of DVT (as defined by those occurring on days 3 or 7). The secondary outcomes were death and duration of hospitalization. The risk factors studied included those related to the pre-existing comorbidities, current illness and interventions in the MICU.

RESULTS: This study was done in a tertiary care hospital, on 219 patients who were admitted in the MICU, between June 2013 and April 2014. The incidence of DVT in the MICU was 17.2%, (n=35/203, 16 patients had DVT on day 1, and hence excluded). Two thirds were catheter associated DVTs (23/35). There was no significant difference in the mortality (9/35 vs. 40/168, p=0.81), although the median duration of hospitalization at discharge (20.5 vs. 10.5 days) was longer for the DVT group. Central venous catheters (RR=15.97, p = 0.01) emerged as the sole risk factor independently associated with the development of DVT in the MICU.

CONCLUSION: There needs to be a low threshold for suspicion of DVT in the MICU. Administration of standard thromboprophylaxis and periodic ultrasound Doppler screening for the same helps in improving outcomes. Appropriate use and timely removal of central venous catheters is important to reduce the occurrence of DVT.

Keywords: deep venous thrombosis, medical intensive care unit, central venous catheters

INTRODUCTION

Deep venous thrombosis (DVT) is frequent among critically ill patients, the risk arising from immobilization, co-morbidities and interventions in the form of mechanical ventilation and central venous catheters. The incidence of DVT in the medical intensive care unit (MICU) was reported to be around 30% before thromboprophylaxis became part of routine care(1,2). 30-50% of untreated DVTs develop into pulmonary embolism (which is fatal in 10-12% of hospitalized cases) and when treated, the numbers significantly reduce to 2-4%.(3) Asymptomatic DVTs and upper limb thrombi likewise, which were initially thought to be of no relevance, have now been found to play a role in decreasing the long term survival of the patients.(4)(5,6)

Current protocols incorporate DVT prophylaxis as a part of standard practice for ICU patients. It is still unclear, if these measures have significantly impacted the development of deep venous thrombosis, though it has been shown in a Canadian study that increased adherence to thromboprophylaxis by 10%, results in 16 fewer deep venous thrombotic events and one fewer pulmonary embolus (7).

Further, there are limited studies on venous thrombosis in critically ill hospitalized medical patients in India.(8,9) Although it has been the perception that Indian patients may be at a lower risk of venous thrombosis, in view of a lower frequency of mutations predisposing to thrombosis; recent multinational worldwide trials have suggested that Indian patients are almost at the same level of risk as that of the western population, and that thromboprophylaxis is largely underutilized in India.(11) . This study attempts to fill these gaps in knowledge by assessing the incidence of deep venous thrombosis in the medical intensive care unit and determining the risk factors associated with development of the same in critically ill hospitalized medical patients.

AIMS AND OBJECTIVES

AIM OF THE STUDY

To study the occurrence of deep venous thrombosis in hospitalized critically ill medical patients in Christian Medical College, Vellore and to assess the factors associated with its development.

OBJECTIVES

1.To determine the incidence of deep venous thrombosis in the medical intensive care unit, Christian Medical College, Vellore.

2.To assess the risk factors playing a role in the development of deep venous thrombosis in the medical intensive care unit, Christian Medical College, Vellore.

LITERATURE REVIEW

DEFINITION

"Thrombus" is defined as a stationary blood clot lodged in the blood vessel, frequently causing vascular obstruction.(10) "Deep venous thrombosis" refers to a blood clot in the major veins of the body, especially in those of the pelvis or lower limbs. Pulmonary embolism is a fatal complication arising from the disruption of the clot and its travel through the venous circulation, to get lodged in the pulmonary vasculature.(11) Deep venous thrombosis also results in post thrombotic or post phlebitic syndrome, as a long term sequele. Venous thromboembolism is a term that includes both, deep venous thrombosis and pulmonary embolism, which in itself, is a sequele of the former. (12)

HISTORY

The first well documented case of DVT dates back to the Middle Ages (1271), where the presentation was characterized by unilateral ankle edema. Thereafter, the number of cases increased steadily, especially being reported among the pregnant and postpartum women.(13) DVT was thus, discovered in the 13th century(14), primarily as a phenomenon occurring in the pregnant women, who were therefore encouraged to breastfeed to prevent the same. It was, for this reason, also called "milk leg".(15) In 1856, Rudolph Virchow proposed the Virchow triad to explain the pathogenesis. Nearly a century later, the pharmacological therapy for the same was introduced. Diagnostic modalities for DVT were also developed during the twentieth century, with the ultrasound Doppler, a relatively simple and less time consuming technique, deserving a worthy note of mention for its role in diagnosis of the same.(16)

GLOBAL EPIDEMIOLOGY – DVT in the World

The annual incidence of DVT is estimated at 1-3 per 1000 adult population.(17) In the United States of America, 3,00,000-6,00,000 patients suffer from DVT every year. Half of these patients develop post thrombotic syndrome and one third develop recurrence of venous thromboembolism over the subsequent 10 years.(18)

Venous thromboembolism related deaths are estimated to occur at 1,00,000-3,00,000 per year. Pulmonary embolism was declared by the US Surgeon General as the most common preventable cause of death among hospitalized patients in the United States.(12) Pulmonary embolism attributes to 60,000 – 1,00,000 deaths in the United States every year. One quarter of patients with pulmonary embolism present with sudden death and 10-30% experience death within the first month of diagnosis.(18) In Europe, 3,70,000 deaths occur annually due to pulmonary embolism.(12)

One study conducted at Boston, similar to our proposed research scheme, at a time when thromboprophylaxis was not part of routine care in the intensive care setting, showed that the incidence of DVT in the MICU was as high as 33%. Though this study was done nearly two decades ago, it is unique in two aspects – 1) it was a prospective study, as compared to many other studies which were done on DVT, at the same time, all of which were retrospective and 2) it looked at upper extremity, lower extremity and central venous catheter related thrombosis, unlike most other studies which looked only at proximal lower extremity thrombosis. (1)

The ENDORSE study, aimed at estimating the proportion of hospitalized patients at risk for deep venous thrombosis and the access to and adequacy of prophylaxis in the same, determined that 36-73% of hospitalized patients all over the world, were at risk of developing deep venous thrombosis; among whom 2-84% received prophylaxis. Among the hospitalized medically ill patients, 21-71% of patients were at risk of deep venous thrombosis.(19) Therefore, it was seen that although, there was a large

proportion of hospitalized patients, who were at risk for development of DVT, thromboprophylaxis was still largely underutilized even in the current era.

INDIAN SCENARIO – DVT in India

The annual incidence of DVT in India is estimated to be at one percent of adult population above the age of forty years and 15-20% among hospitalized patients. One percent of cases with DVT develop pulmonary embolism. One out of every two hospitalized patients in India are at high risk for developing venous thromboembolism at any point of time.(20)

A retrospective study done in South India, showed that the incidence of DVT was 17.46 per 10,000 hospital admissions.(21) Therefore, in contrast to the popular belief earlier, that Indian patients were at reduced risk for development of DVT, studies have shown that the risks are similar to that in the other parts of the world. The ENDORSE study showed that 45% of hospitalized medically ill patients in India are at risk of DVT; among whom, only 22% received thromboprophylaxis.(19) This study showed that the need for thromboprophylaxis is largely underestimated in India.

Indian studies have shown that the incidence of DVT among hospitalized critically ill medical patients range from 3% to 13.5%.(9,22) However, there have been no uniform protocols regarding thromboprophylaxis in these studies and as a result, the thromboprophylactic measures are inadequate and incomplete. There is paucity of data on studies which have been done on standard thromboprophylaxis protocols.

PATHOPHYSIOLOGY

In 1856, Rudolph Virchow attributed thrombus formation to the interplay between the factors of the Virchow's triad, namely endothelial injury, hypercoagulability and alteration in blood flow (stasis in veins, and turbulence in arteries).(12)

Recent studies have led to the refinement of Virchow's initial proposed model. Activated coagulation is the primary etiological factor in venous thrombosis; while stasis is largely regarded as a permissive factor. The concept of venous injury has expanded to include molecular changes occurring at the level of the endothelium. The natural history of acute deep venous thrombosis is now thought of, largely as a balance between recurrent thrombotic events and processes aimed at restoring the venous lumen.(23)

The thrombus formed in the proximal deep veins of the legs can migrate to the pulmonary circulation and get lodged in the pulmonary arteries resulting in the dreaded sequele, pulmonary embolism. Isolated thrombi in the calf veins are smaller and are more commonly involved with paradoxical embolism to the systemic circulation, in the presence of septal defects. With increase in the use of central venous catheters, upper extremity thrombi have also become fairly common in the hospitals of today, the clinical significance of which was hardly known.(12) Recent studies have shown that the majority of upper extremity thrombi are catheter associated and resolve spontaneously; with the risk of embolization being 2%.(5)

DVT can be fatal when it leads to pulmonary embolism or can cause delayed complications among survivors like chronic thromboembolic pulmonary hypertension and post phlebitic syndrome.(12)

Pulmonary hypertension results from increased vascular resistance distal to the embolus and is often distressing as it amounts to a significant degree of breathlessness on exertion.(12)

Post phlebitic syndrome, also known as chronic venous insufficiency, results from the incompetence of the venous valves which occurs secondary to a long standing deep venous thrombus. It is disabling, as it results in swelling, pain and ulcers over the legs.(12)

PREDISPOSING FACTORS (12)

Co morbidities:

Cancer

Chronic Obstructive pulmonary disease

Hypertension

Pregnancy

Surgery

Trauma

Previous venous thromboembolism(24)

Hospitalization(25)

Neurological diseases with paralysis, e.g.: stroke(25)

Thrombophilias

Inherited:

Factor V Leiden mutation

Protein C deficiency

Protein S deficiency

Antithrombin III deficiency

Acquired:

Antiphospholipid antibody syndrome

Admission to intensive care units(1)

(Risk factors unique to ICU stay are as follows)

Central venous catheters(26)

Peripherally inserted central venous catheters(27)

Mechanical ventilation

Sedatives

Muscle relaxants

Vasopressors

Transfusions

Lifestyle:

Long haul air travel

Smoking

Red meat

Drugs:

Oral contraceptive pills

Hormone Replacement Therapy

IMPACT OF DEEP VENOUS THROMBOSIS

DVT is a frequently encountered problem in hospitalized patients.(1,19,25) It contributes to a large proportion of hospital acquired mortality (in the form of pulmonary embolism) and morbidity (in the form of post phlebitic syndrome and thromboembolism pulmonary hypertension).(12) One community based study had shown that the in-hospital case fatality rate of venous thromboembolism was 12%, and among those discharged, the long term case fatality rates were 19%, 25%, and 30% at 1, 2, and 3 years after discharge respectively.(28) It was always thought of as a disease of the western population; but recent studies have shown that the risk of deep venous thrombosis among hospitalized patients is almost comparable between India and the west.(19)

HEALTH CARE COSTS OF VENOUS THROMBOEMBOLISM

Western studies have shown that the development of an in-patient DVT, pulmonary embolism or both results in additional costs of $8000, $14,000 and $28,000 over and above the final bills of general medical patients.(30) The annual health care costs implicated in hospital acquired DVTs was estimated to range between 6.8 and 36 billion US dollars in the United States of America.(31) Studies have also shown that the presence of DVT leads to increase in the length of ICU stay and hospital stay, thereby, draining the health care resources. (26)

DEEP VENOUS THROMBOSIS IN THE MEDICALLY ILL

There is an increase in the number of hospitalized medical patients at risk for development of DVT, than the surgical patients.(12) Recent studies have shown that the risk for development of DVT was slightly and surprisingly higher among medical patients as compared to surgical patients (6.48 vs. 5.0).(32) Several studies have been done in the western population on DVT in the hospitalized critically ill medical patients. Studies done during the last two decades have demonstrated a higher

than anticipated prevalence of deep venous thrombosis among these patients.(1,33–35) Most of these studies were retrospective in nature; and therefore limited data was available on the unique factors playing a role in the development of deep venous thrombosis in the intensive care setting.(26,36) An Indian study has shown that 75% of patients admitted to the general medical wards and intensive care units are at high risk for development of DVT.(8)

DEEP VENOUS THROMBOSIS IN THE INTENSIVE CARE SETTING

The incidence of DVT amongst hospitalized medically ill patients in the intensive care setting was reported to be as high as 33% in the pre-thromboprophylaxis era.(1) This has come down to 15% after initiation of thromboprophylaxis, as reported by most of the recent studies.(33,35,37)

A Canadian study done amongst critically ill, medical and surgical patients (more than two thirds of which were medically ill, non-surgical patients), in the intensive care setting, showed that the prevalence of DVT was 5.37%. But the thromboprophylaxis coverage in this study was only 62.5%.(26) A recent Chinese study assessed the need for thromboprophylaxis by studying the incidence of DVT in the intensive care unit. It was estimated to be 19% in the absence of thromboprophylaxis.(33) Another study, based in the intensive care unit, in Beijing, determined the incidence of DVT to be 15.1%, with 7.5% having suspected pulmonary embolism, and 1.7% having confirmed pulmonary embolism.(35) A study in Thailand, estimated the incidence of DVT in the MICU to be 8.82%, with incomplete thromboprophylaxis coverage.(37) A retrospective study from Iran, determined the incidence and prevalence of proximal lower limb DVTs in the medical and surgical intensive care units to be 5.2% and 9.4% respectively.(38)

It was seen from the above studies that, the incidence of DVT in the intensive care setting is highly variable (5-15%), especially in the medically ill patients. This discrepancy can be largely

attributed to the absence of standard protocols for thromboprophylaxis in most medical intensive care units, as a result of which there is a wide variation in the implementation of the same.

However, with recent guidelines insisting on implementation of thromboprophylaxis (either pharmacological, or mechanical in the event of contraindications for the former) as part of standard care in the intensive care setting, there have been a few studies which looked at the occurrence of DVT amongst patients on standard thromboprophylaxis.

A study from Washington, USA, done in the MICU, to determine the presence of DVT in patients requiring prolonged mechanical ventilation (>7 days), estimated an incidence of 23.6% despite 100% thromboprophylaxis coverage.(39) Another study from Massachusetts, USA, showed that the incidence of proximal lower limb DVTs was 12% despite 92% thromboprophylaxis coverage.(40) These studies were limited by the small numbers of patients being studied.

The PROTECT trial was a large multicentric trial done on patients in the intensive care units. This was a randomized controlled trial done to compare the efficacy of unfractionated heparin vs. low molecular weight heparin (dalteparin was chosen as it was safe in renal dysfunction) in preventing proximal lower limb DVTs. All patients were randomized to receive unfractionated heparin or dalteparin as part of their thromboprophylaxis and the median duration of receiving thromboprophylaxis was for a week. It was seen in this study that, despite 100% thromboprophylaxis coverage, the incidence of proximal lower limb DVT was overall 5.47% (5.1% in the dalteparin group vs. 5.8% in the heparin group), with the incidence of pulmonary embolism being 1.79%. 88.7% of the DVTs and 70% of the pulmonary emboli were detected during the ICU stay, implying that the largest risk of development of DVT in hospitalized patients was within the intensive care setting.(41)

As most of the afore mentioned studies have only focused on the presence of proximal lower limb DVTs, these figures could largely underestimate the total venous events (inclusive of the upper

extremity and axial venous thrombosis (like splanchnic and cerebral vein thrombosis)) occurring in the intensive care setting, which could also influence the mortality and morbidity of these patients.

Upper extremity thrombi have been reported only by a few DVT studies. One of the earlier studies, done in the pre-thromboprophylaxis era, determined the incidence of upper extremity DVTs in the MICU to be 5%.(1) The PROTECT trial showed that the incidence of non leg DVTs, while on thromboprophylaxis, was 2.2%, with 94.5% of them originating in the upper limbs.(42)

Deep venous thrombosis in the Indian subcontinent is a topic where recent exploration has begun. Several studies have been done on DVT in hospitalized surgical patients in India; in contrast to the paucity of studies done on medical patients. A study has shown the incidence of DVT among hospitalized medical patients (in the general medical wards and intensive care units) to be around 3% in India. These patients were not on standard thromboprophylaxis.(9) Another study which looked at the thromboprophylaxis and patients at risk for DVT amongst those admitted in the general medical wards, showed that the initiation of thromboprophylaxis within the first few days of admission had been seen only in 12.5% of patients. Further, 72% of patients who required hospitalization beyond two weeks were found to be at high risk for DVT.(8) Thus, thromboprophylaxis is largely underutilized in India. There have not been any studies in India which have attempted to explore the frequency of DVT, in hospitalized critically ill medical patients on thromboprophylaxis, and the risk factors unique to a medical intensive care setting.

FACTORS ASSOCIATED WITH DEVELOPMENT OF DVT IN THE MICU

The risk factors studied for deep venous thrombosis include:

Host factors: elderly age group, female gender, obesity(37,40)

Co-morbidities: Malignancy, surgery, trauma, pregnancy, post-partum, hospitalization, previous venous thromboembolic events, hospitalization, thrombophilias, pacemakers, varicose veins, air-travel, renal failure, chronic obstructive pulmonary disease, congestive cardiac failure, neurological diseases.(25,40,43)

Addictions: Smoking, Alcohol(12)

Drugs: hormone replacement therapy, oral contraceptive pills(12)

ICU related: central venous catheters, peripherally inserted central venous catheters, mechanical ventilation, use of sedatives, muscle relaxants & vasopressors, dialysis and transfusions(25,26,35)

DIAGNOSIS OF DEEP VENOUS THROMBOSIS IN THE CRITICALLY ILL

The modalities for diagnosing DVT have also evolved from complex, time-consuming techniques like phlebography, impedance plethysmography, and magnetic resonance venography, to simpler, bedside, cost effective tools like the Doppler and compression ultrasonography.(43) Several studies have shown that the compression ultrasound is a highly sensitive and specific tool for bedside diagnosis of DVT by criticare physicians.(44–46) It is not only time-saving, but also cost effective, easily accessible, and a simpler technique to master. Compression ultrasound, when compared to the duplex ultrasound, has a sensitivity of 88.9%, specificity of 75.9% and a negative predictive value of

95.7%.(47) The sensitivity and specificity of compression ultrasound in the hands of criticare physicians as a screening tool for DVT has been estimated at 100% and 99% respectively.(45)

DEEP VENOUS THROMBOSIS PROPHYLAXIS

Studies in surgical patients had shown that thromboprophylaxis was effective against the development of DVT. A study done in a neurosurgical intensive care unit, showed that the rate of occurrence of DVT came down from 16% to 9% by institution of pharmacological thromboprophylaxis, with a relative risk reduction of 43%.(34) Studies amongst medically ill patients, have however, shown an incidence of 15-30% of DVT despite the prophylaxis,(1,2,35) which led to questions being raised on the rate of implementation, adherence, cost effectiveness and adequacy of thromboprophylaxis.(1,1,7,19,26) Factors associated with institutionalization independently account for more than half the cases of DVT in the community, and this has also led to a greater need for emphasis on thromboprophylaxis.(49) All of this, has paved way to the ACCP guidelines for thromboprophylaxis. The recent ACCP guidelines (2012) state that all critically ill patients are to be considered at high risk for DVT, and hence to be started on thromboprophylaxis.(50)

A NOTE ON THE 2012 ACCP GUIDELINES FOR THROMBOPROPHYLAXIS IN MEDICAL PATIENTS

1) Low risk patients – No need for prophylaxis
2) High risk patients (including *all critically ill* patients)
    a. Without bleeding or its risk – pharmacological prophylaxis with unfractionated heparin, low molecular weight heparin or fondaparinaux
    b. With bleeding or high risk of it – mechanical prophylaxis with intermittent pneumatic compression or graduated compression stockings (as the risk for bleeding decreases, the patient can be switched to pharmacological prophylaxis)

3) Incidental thrombophilia
    a. With history of previous venous thromboembolism – thromboprophylaxis is essential (for lifelong)
    b. Without history of previous venous thromboembolism – no need for prophylaxis
4) Out patients with malignancy
    a. With other risk factors for venous thromboembolism – Daily thromboprophylaxis
    b. Without other risk factors for venous thromboembolism – No need for prophylaxis
5) High risk patients on long haul flights – walking, calf muscle exercises, compression stockings.(50)

Therefore, by the turn of the last decade, deep venous thrombosis was largely considered a preventable disease, widely prevalent among hospitalized patients, contributing to a large share of mortality and morbidity worldwide and in India, and the need for its prophylaxis was grossly underestimated.(19)

RELEVANCE OF THE RESEARCH TOPIC

Deep venous thrombosis is a major public health problem in the global and Indian scenarios. The proportion attributed to hospitalization is largely preventable. A large number of studies in the western population have described the disease frequency and the associated risk factors and have thereby resulted in the formation of guidelines for diagnosis, prophylaxis and management of the same, which are also being practiced in India.

There has been a steady increase in the number of studies on deep venous thrombosis in the Asian population, over the last decade, with the major contributions coming from China and Thailand. (33,35,37) Indian studies on deep venous thrombosis are limited. (8,9)

There are only a few studies which have looked at both, upper and lower extremity thrombi(1); as most studies generally tend to focus on the lower extremity thrombi because of their implications in the form of pulmonary embolism and therefore mortality. Recent studies have shown that upper extremity thrombi also contribute to pulmonary embolism (in lower frequency) and reduced overall long term survival.(5,6) In view of the increasing trend in the use of central venous catheters and peripherally inserted central venous catheters and therefore, a higher than anticipated incidence of upper limb thromboses, it was decided to specifically look for upper extremity and lower extremity thromboses during every screening in the study, so as to be able to unify the pathophysiological factors playing a role in the development of deep venous thrombosis, irrespective of the site.

Recent multinational worldwide trials have shown that the Indian hospitalized patients are almost at the same level of risk as that of the western population, and thromboprophylaxis is largely underutilized in India.(19) This prompted us to do research on this sparsely explored field.

The incidence and risk factors of deep venous thrombosis in hospitalized *critically ill* medical patients in India have not been assessed in the past. This study is aimed at determining the disease frequency in a high risk population (hospitalized critically ill medical patients in the intensive care unit) in a standard protocolized environment (on thromboprophylaxis), which will in turn reflect on the need and adequacy of thromboprophylaxis in India. The study also hopes to describe risk factors unique to the Indian population in the intensive care setting, for development of deep venous thrombosis; assessment and evaluation of which might modify the guidelines for its management, in order that they are more endogenous and appropriate to the Indian population. It might also help us to better understand the role of various factors in the pathogenesis of DVT.

METHODS

SETTING

This study was done from June 2013 to April 2014 in the Department of General Medicine, Christian Medical College, Vellore, at the medical intensive care unit and high dependency unit.

Christian Medical College, Vellore, is a 2695 bedded multispeciality hospital and medical college which caters to 1.9 million out-patients and 1.2 lakh in-patients annually and 5500 out-patients, 2500 in-patients, 75 surgical procedures, 22 clinics and 30 births on a daily basis.

The Medical Intensive Care Department functions as a 24 bedded complex that includes the Medical Intensive Care Unit and the Medical High Dependency Unit, with 12 beds in each. There are 1500-1600 admissions on a yearly basis and 100-120 admissions on a monthly basis, with more than two thirds of the admissions requiring mechanical ventilation, and around half the patients requiring more than one week of stay in this setting. Around half of these patients belong to the department of medicine, while the remaining stream of patients stem from various medical superspecialities like hematology, rheumatology, gastroenterology, neurology, nephrology, endocrinology and cardiology. The mortality rate in the medical intensive care unit and high dependency unit, is around 25%.

STUDY DESIGN

A prospective observational cohort study design was adopted to determine the incidence and risk factors for the development of deep venous thrombosis in the Medical ICU.

The primary objective of the study was to determine the incidence of deep venous thrombosis in the hospitalized, critically ill medical patients, despite adequate thromboprophylaxis. Therefore, a prospective study design, was considered appropriate to assess the primary objective.

This study was done entirely in patients belonging to the unit of Medicine, getting admitted to the Medical ICU. This gave us the opportunity of studying an exclusive cohort of patients in a standard protocolized environment. The secondary objective was to assess the risk factors for development of DVT in this group of patients. Hence a prospective cohort study was considered ideal for determination of incidence and risk factors for deep venous thrombosis in this cohort of hospitalized patients in the medical intensive care setting.

PATIENTS

INCLUSION CRITERIA

All patients belonging to general medicine, above the age of 16 yrs, admitted in the medical intensive care unit and the medical high dependency unit between June 2013 and April 2014 were included in the study.

EXCLUSION CRITERIA

1) Patient/caregiver refusing consent for entering the study
2) Admission diagnosis of Deep venous thrombosis / Pulmonary embolism
3) Patient already on therapeutic anticoagulation, e.g.: prosthetic heart valves
4) Readmission to MICU/MHDU within a single hospital stay

Patients who had died or who had been discharged from the hospital within 48hrs of admission into the medical intensive care unit or high dependency unit, were also excluded from the study, post inclusion. Patients who got transferred to the wards before they were screened with their day 3 & 7 ultrasound Dopplers, were followed up and screened in the ward on the respective days. Those who had got discharged before their day 7 ultrasound, were considered as lost to follow up for the last follow up scan.

PROTOCOL IMPLEMENTATION

A protocol for thromboprophylaxis (Appendix 1) has been in place in our medical intensive care unit and medical high dependency unit. The protocol was created by Dr.George John, Professor and Head, Medical Intensive Care Unit and is being followed since 3-4 years.

ULTRASOUND TRAINING OF THE INVESTIGATOR

The principal investigator (self) was trained in compression ultrasound for detection of deep venous thrombosis by Dr. Kishore Pichamuthu, Associate Professor, Medical Intensive Care Unit, over a period of 2 weeks. Dr. Kishore was trained in critical care sonology in Westmead Hospital ICU, Sydney. He has designed a website on critical care echocardiography and ultrasound (www.criticalecho.com). He is also involved in the training of students and faculties in ICU sonology in CMC hospital, Vellore and conducts annual hands-on workshop on ICU sonology.

ULTRASOUND TECHNIQUES USED

Ultrasonography is the current first-line imaging examination for deep venous thrombosis (DVT) because of its relative ease of use, absence of irradiation or contrast material. Previously quoted studies have shown superior sensitivity and specificity for the compression ultrasonography for the diagnosis of DVT, even in the hands of emergency and criticare physicians.

ULTRASOUND MACHINE AND THE VASCULAR PROBE

M-Turbo Ultrasound machine (Sonosite) [dynamic range up to 165 dB] is the bedside ultrasound machine that was used for the study. The high frequency catheter probe (gives high resolution of images near the body surface and hence), preferred for vascular imaging, was used for the diagnosis of DVT in this study. It resembles a tiny leg and foot, with the transducer being present in the foot region. It has a frequency range of 7-12 MHz and has colour flow imaging and pulse wave Doppler.

Ultrasound Machine (to the left)

Vascular probe (below)

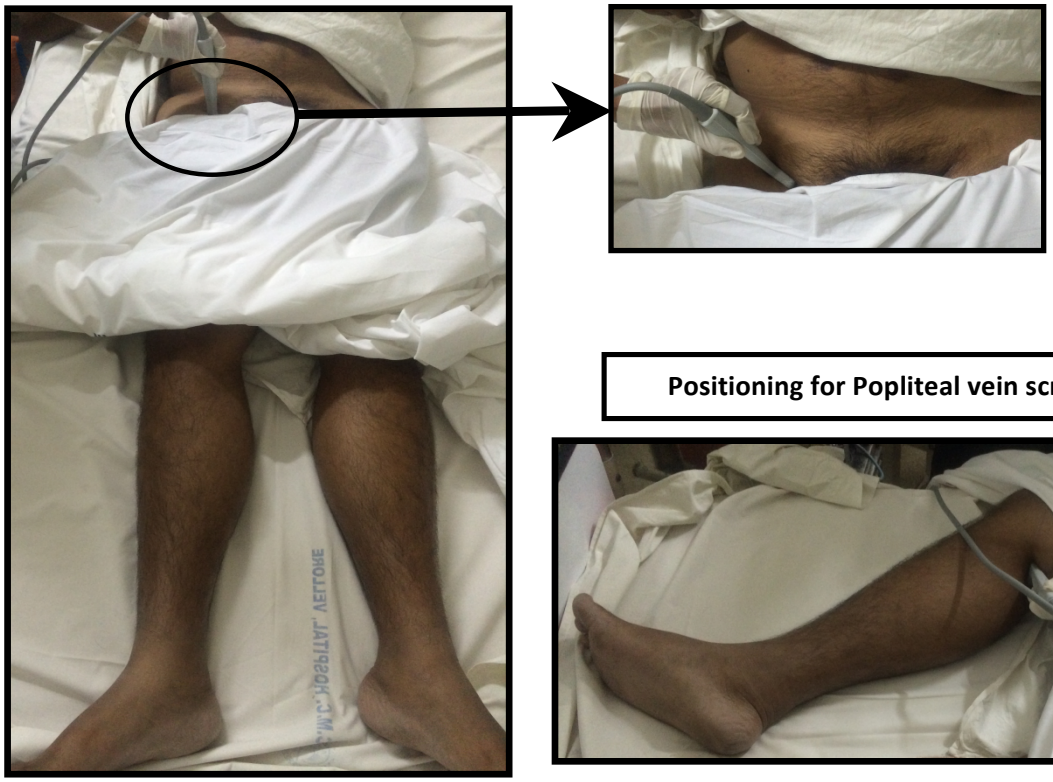
POSITIONING OF THE PATIENT AND THE PROBE

For the assessment of lower limb DVT, the patient is supine with the legs exposed up to the inguinal ligament. Bedside ultrasonography for lower limb deep vein thrombosis (DVT) is performed at 2 principal sites, one on each side – the femoral and the popliteal. Ideally, 30-40 degrees of reverse Trendelenburg facilitates the examination by increasing venous distension. The probe is held with its long axis (of the foot – transducer region) perpendicular to the axis of the vessel being studied.

When examining the femoral vein, the patient's hip is externally rotated and flexed for better and easy visualization. The probe is placed at the mid inguinal point, just below the inguinal ligament. The vein is located medial to the artery at this point. When examining the popliteal vein, the popliteal fossa on the posteromedial aspect of the knee is exposed by bending the knee and externally rotating the hip. At the popliteal fossa, the probe is placed and the vein lies superficial to the artery here.

The assessment of upper limb DVT is also done in the supine position, in 2 principal sites, namely, the jugular and the axillary. For this, the Trendelenburg position facilitates better visualization of the upper limb veins due to venous distension. When examining the jugular vein, the patient's head is turned towards the opposite side and the probe is placed along the anterior border of the sternocleidomastoid at the junction of upper two-thirds and lower one-third. The vein is usually superficial to the artery here. When examining the axillary vein, the patient's arm is extended and abducted and the probe is placed at the axilla towards the apex and manoeuvred until visualization of the axillary vessels is made. The position of these vessels is highly variable.

Positioning for Femoral vein screening



Positioning for Popliteal vein screening

Positioning for Jugular vein screening

Positioning for Axillary vein screening

IDENTIFICATION OF THE VEIN FROM THE ARTERY

The vein is differentiated from the artery based on 5 sonological attributes:

Sonological Characteristics	Vein	Artery
Shape	Ovoid	Round
Pulsatility	Absent	Present
Compressibility	Present-Walls meet each other	Absent-Stays open
Colour flow imaging*	Continuous undulating flow	Intermittent pulsatile flow
Pulse wave Doppler	Steady gradually changing flow	Accelerating pulsatile flow

*In colour flow imaging, identification of the artery and vein merely based on the colours red and blue, respectively is not advisable, as the colours can be altered by changing the direction of angulation of the probe.

DETERMINATION OF DVT

The following techniques have been described for the determination of DVT, although only lack of compressibility and direct visualization of the thrombus was used in DVT diagnosis in our study.

COMPRESSIBILITY

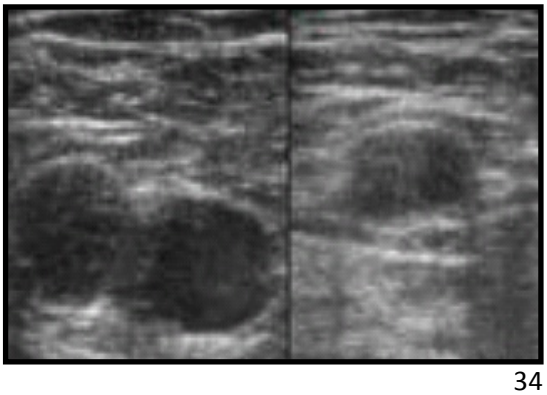
After identification of the vein, pressure is applied vertically downward, on the transducer, without changing the position of the probe, with the vein being visualized at the centre of the image window. The pressure is applied until the vein collapses completely. The artery is generally more resistant to deformation and hence, does not collapse.

In case of a patent vein with normal flow, the lumen collapses completely and the walls touch each other; while the artery beside, is usually still open and pulsatile. Subsequently, the pressure on the transducer is relaxed and the vein is allowed to resume to its normal shape. The amount of pressure required to collapse a vein will vary from patient to patient, and with experience, it is easy to ascertain whether adequate pressure has been applied.

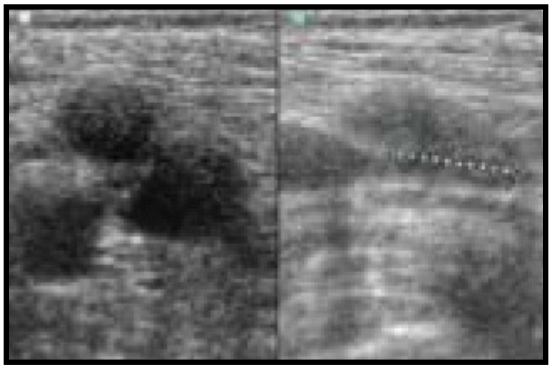
Compressibility indicates lack of thrombus in the vein at that particular region. Ideally, this needs to be done along the entire length of the vein. As this is cumbersome and time-consuming, there have been studies which had looked at the utility of compression ultrasound at a few points along the course of the vein. Studies have showed good sensitivity and specificity (100% and 99% respectively) for the 2 point compression ultrasound (at common femoral and popliteal) in the hands of emergency physicians in diagnosis of DVT. In our study, only this technique was applied at eight points (bilateral jugular, axillary, femoral and popliteal) to detect the presence of a thrombus.

Non compressibility of the vein, even at pressures where the artery starts to deform, is indicative of a thrombus. Non compressibility must be interpreted with caution because downward pressure at the wrong angle or down the wrong vector can greatly decrease the actual pressure felt by the vein and can make it appear non compressible.

Compressibility of the Femoral Vein



Non compressible – thrombus visualized



PHASICITY

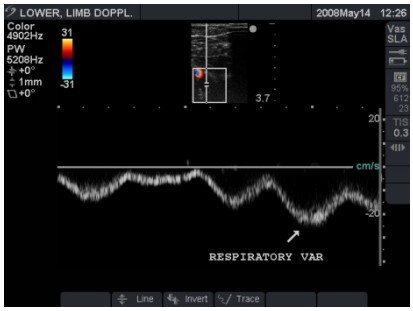
After visualizing the vein and positioning it at the centre of the image window, the probe is angulated downwards and the curser of the pressure wave Doppler is placed at the centre of the venous lumen. In the Doppler mode, a pressure wave tracing is obtained, which shows cardiac and respiratory variations. The respiratory variations are more pronounced.

In spontaneously breathing patients, there is an increased flow during inspiration, while the reverse occurs in mechanically ventilated patients. Absence of such variation usually signifies proximal thrombosis (between the point being tested and the inferior vena cava). This technique was not applied in our study.

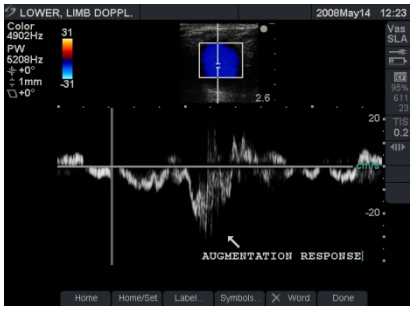
AUGMENTATION

The pulse wave Doppler or the colour flow imaging can be used to assess augmentation. After visualization of the vein and activation of the pulse wave Doppler tracing, the calf muscles are gently squeezed and this results in surge of blood flowing through the vein. This causes peaking of the tracing in a normal patent vein. If colour flow imaging is activated, it causes an increased flow as visualized by a splurge of colours on the imaging. Absence of this response indicates presence of thrombus between the point being studied and the calf. This technique was also not used in our study.

Phasicity



Augmentation



DIRECT VISUALIZATION OF THROMBUS

In a few cases, the thrombus can be visualized as a slightly echogenic mass inside the vein lumen. It may be sessile, fixed to the wall or be floating in the flow, tethered at one point to the wall. A chronic organized thrombus appears more echogenic and is firmly attached to the wall. The degree to which the lumen is obstructed is variable.

All the aforementioned techniques have been traditionally described for assessment of lower limb DVT. In our study, we utilized the principles of compressibility and direct thrombus visualization for making a diagnosis of DVT. In the event of absent compressibility, the presence of a thrombus was further confirmed with phasicity and augmentation. These techniques were used for detection of upper limb and lower limb DVT at four points, where compressibility was assessed (jugular, axillary, femoral and popliteal). In the event of direct thrombus visualization, compressibility was not done for fear of proximal embolization.

SAMPLE SIZE CALCULATION

The sample size was estimated to be 196 with the presumed incidence of deep venous thrombosis being 15% (35) amongst patients admitted in the medical intensive care unit. Sample size was calculated using this incidence of 15%, confidence intervals of 95% and margin of error being 5%.

Sample size was calculated by the formula $\frac{Z(1\text{-alpha})*Z(1\text{-alpha})*P*Q}{D*D}$

Where Z (1-alpha) is the confidence interval (1.96)

P is the prevalence (15%)

Q is [1-P] (85%)

D is the precision (5%)

Sensitivity table was drawn for an expected incidence of 15%.

Prevalence (P)	15	15	15
Alpha	0.05	0.05	0.05
Z(1-alpha)	1.96	1.96	1.96
Precision	5	4	3
Calculated sample size	**196***	**306**	**544**

It was seen from the sensitivity table that, for a higher precision, a larger sample size was required for the same prevalence and confidence intervals. For feasibility constraints, it was decided to work on the sample size calculated using 5% precision (n=196).

Sample size was also calculated for risk factor analysis by considering two important risk factors associated with deep venous thrombosis in the intensive care setting – namely mechanical ventilation and central venous catheters(25) – to ensure adequacy of the above calculated sample size for the risk factor analysis.

	Mechanical Ventilation	Central Venous Catheters
Proportion of disease among unexposed (40)	0.42	0.03
Relative Risk (25)	1.5	5
Proportion of disease among exposed	0.63	0.15
Power (1- beta) %	80	80
Alpha error (%)	5	5
1 or 2 sided	2	2
Required sample size in each group	88	88

RELIABILITY EXERCISE – KAPPA VALUE FOR AGREEMENT

Reliability exercise was done to determine the rate of inter-observer agreement, prior to initiation of the study. This was planned using the Cohen's kappa co-efficient. This was done with three observers: principal investigator (self), co-investigator (Dr. Thomas, Assistant Professor, Medical Intensive Care Unit) and a radiologist (Dr.Balaji, Assistant Professor, Dept of Radiology).

Statistician was consulted and it was decided to perform the reliability exercise on 10% of the sample size. As the sample size calculated was 200 and as each patient was planned 3 ultrasound scans over a week of admission, it was decided to perform 60 scans (200 X 3 = 600 – 10% = 60) for the reliability exercise. Ideally, replicating the study design, each of the observers had to study the same 20 patients in the MICU, performing 3 scans over 1 week on each of the patients. But for feasibility and ease of conducting the reliability exercise, it was instead decided to perform one ultrasound each on sixty different patients admitted in the Medical ICU.

This study was done over a period of 10 days and six patients were studied per day. The study patients were allotted by a consultant in the MICU. Compression ultrasound was done on eight points in each of these patients (bilateral jugular, axillary, femoral & popliteal). Each of these patients was scanned by all the three observers at different times in the same day and the observations were recorded independently. At each of these points, the presence of DVT was assessed by each of these observers, based on compressibility and thrombus visualization. As the turnover and the mortality rates in the MICU were high, some of the patients who were scanned by one observer were missed by the others (primarily due to death or discharge against medical advice). Therefore, only 48 patients were finally assessed, as data on the others were incomplete due to the aforementioned reason.

The data from these 48 patients were analyzed from all the three observers and kappa value for agreement was calculated for each of these points assessed and for the overall presence or absence of DVT (Table 1). It was seen that the inter-observer agreement was almost perfect at all sites other than jugular (fairly good for jugular). The agreement was substantial for the overall presence of DVT. The agreement was statistically significant for all parameters.

Kappa's Inter-observer variation:

Site (n=48)	Kappa value*	P value
Right Jugular	0.64	<0.001
Left Jugular	0.49	<0.001
Right Axillary	1.00	<0.001
Left Axillary	1.00	<0.001
Right Femoral	1.00	<0.001
Left Femoral	1.00	<0.001
Right Popliteal	1.00	<0.001
Left Popliteal	1.00	<0.001
Overall presence of DVT	0.77	<0.001

*Kappa value interpretation:

<0.40 – poor interobserver agreement

0.40-0.75 – fairly good interobserver agreement

>0.75 – excellent inter-observer agreement

DATA COLLECTION

The protocol was submitted before the initiation of study and was approved by the *Institutional Review Board and Ethics Committee (No: 8067)*. Informed consent was obtained from all the participants prior to their entry into the study. All the variables of interest were collected through a data abstraction form (Appendix 2) which was duly filled by the principal investigator (self) on day 1 of admission. The predictor variables related to treatment and outcomes were filled by day 7 of admission, at the time of the last follow up scan, just prior to the patient exiting the study. All the variables used in the data abstraction form were clearly defined prior to starting the study, to avoid discrepancies and ambiguity (Appendix 3).

Compression ultrasound was done to detect upper and lower extremity and central catheter related deep venous thrombosis. This was done by the principal investigator (self) and a co-investigator on all participants in the study on day 1, day 3, and day 7 of admission in *MICU/MHDU. The day 1 ultrasound was planned to pick up patients positive for deep vein thrombosis on day 1 of MICU/MHDU admission itself. As we were looking at the incidence of deep venous thrombosis in the medical intensive care unit, in the purest sense, it was decided to exclude patients who were positive on day 1 from the incidence data. In the literature review, it had been seen that the highest risk for development of deep venous thrombosis in an intensive care setting is within the first 48 hours and the second highest is within the first week (1); therefore the timing of the subsequent ultrasound screenings had been planned on day 3 and day 7, so as to not miss the most vulnerable periods for deep vein thrombus development during an ICU stay.

Compression ultrasound was done at four points – axillary, jugular, femoral and popliteal – on each side and at every time. Absence of compressibility or visualization of thrombus was

considered to be positive for deep venous thrombosis. These patients were followed up till the time of discharge for ICU & hospital outcomes.

OUTCOMES STUDIED

PRIMARY OUTCOME

DVT Encountered in the Study: Patients with any one or both of the following features on a screening ultrasound on D1/D3/D7 at any site and at one or more sites examined were considered to have a DVT

1) Lack of compressibility on ultrasound
2) Visualization of thrombus

Incident DVT in the Medical ICU: As the term "incidence" refers to the occurrence of new events in a particular setting, in the purest sense, the day 1 DVTs were not considered as incident DVTs. Incident DVTs in the medical ICU refers to the development of DVT on day 3 or day 7, as detected by the ultrasound screening.

SECONDARY OUTCOMES

Death

ICU death*:* Mortality within the MICU/MHDU, before being transferred to the wards, was considered as death in the ICU.

Hospital death*:* Mortality before discharge of the patient from the hospital was considered as hospital death.

Cause specific mortality*:* All the in-hospital deaths were further categorized based on the etiology into 3 sub-groups:

1) *Sudden death* where the cause was uncertain (pulmonary embolism may be considered as one of the differentials)
2) *Confirmed pulmonary embolism* (by imaging – RA/RV dilatation on ECHO or CTPA based diagnosis)
3) *Other causes* due to established causes other than pulmonary embolism

Discharge

Patients who had been discharged alive from the hospital or from the ICU/HDU itself, in a stable condition, after completion or initiation of treatment.

Discharge against medical advice

Patients who had been discharged against medical advice from the hospital or from the ICU/HDU, before completion of evaluation or management.

Discharge diagnosis of DVT

Patients who had been discharged with a diagnosis of DVT from the hospital, after initiation of oral anti-coagulation.

MEASURES TO REDUCE POTENTIAL BIAS

Detection bias was anticipated, as the principal investigator and the co investigator were physicians (although trained in criticare sonology) and as their findings might differ from those of the radiologist. This bias was reduced by performing a reliability exercise before beginning the study and after ascertaining good inter-observer variation through calculation of the kappa co-efficient (0.77). Recall bias was the other bias that was anticipated to occur during the collection of the exposure variables (with respect to past history). All attempts were taken to minimize this bias by trying to procure evidence in the form documentation, wherever possible, for the history given by the participants.

STATISTICAL METHODS

Analysis was done using SPSS version 16 (Copyright 2007). Data was entered in EPIDATA software with quality control checks such as range and consistency. Data quality was further explored using histogram, Box Cox plots and frequency distributions (which was used for continuous variables). Categorical variables have been presented as numbers and percentages and continuous variables as mean and standard deviation (SD). If the distribution was skewed, besides the mean and SD, Median with interquartile range have also been presented. Categorical variables were analyzed using Chi square test with Yates's correction and Proportion test. Continuous variables were analyzed using Independent sample t test. Non parametric Mann Whitney U test was used when the distribution was skewed. Logistic regression analysis was done to determine the risk factors for DVT with log link. Model assumptions were checked using likelihood residual plots against predicted probability. Goodness of fit of the model was assessed using Hosmer Lemeshow chi-square statistics.

RESULTS

INCLUSION OF PATIENTS AND BASELINE CHARACTERISTICS

There were 259 patients who were screened for eligibility for inclusion into this study, on admission into the medical intensive care unit between June 2013 and April 2014 (Figure 1). Ten patients were excluded as per protocol as they were found to be admitted with a diagnosis of DVT or pulmonary embolism or were already on anticoagulation therapy at the time of admission. An additional 30 patients were excluded post hoc due to death or discharge within the initial 48 hours of admission into the MICU.

There were 219 patients who were finally included into the study. The mean age of this group was 45.3 ± 17.5 yrs and there was a slight male predominance (n=121) (Table 1). The mean SOFA score at admission was 7.2 ± 4.2. Amongst the risk factors being studied, the ones most frequently encountered in this group were: prior hospitalization (n=39, 17.8%), smoking (n=34, 15.5%), and alcohol intake (n=47, 21.5%). Amongst the effect modifiers being studied, treatment with vitamin K, aspirin and clopidogrel was seen in 36 (16.4%), 25 (11.4%) and 19 (8.7%) patients respectively. Only 10 patients had symptoms suggestive of deep venous thrombosis, in the form of swelling (n=5), warmth (n=3), erythema (n=1) and tenderness (n=1). Majority of the patients were on mechanical ventilation (n=164, 74.9%) and central venous catheters (n=154, 70.2%). Femoral and jugular catheters were almost equally distributed in the group of patients on central venous catheters. It was notable that all 219 patients were on thromboprophylaxis during the study.

Figure1:STROBE Figure–Flow of patients into the study

(Study period: June 2013-April 2014)

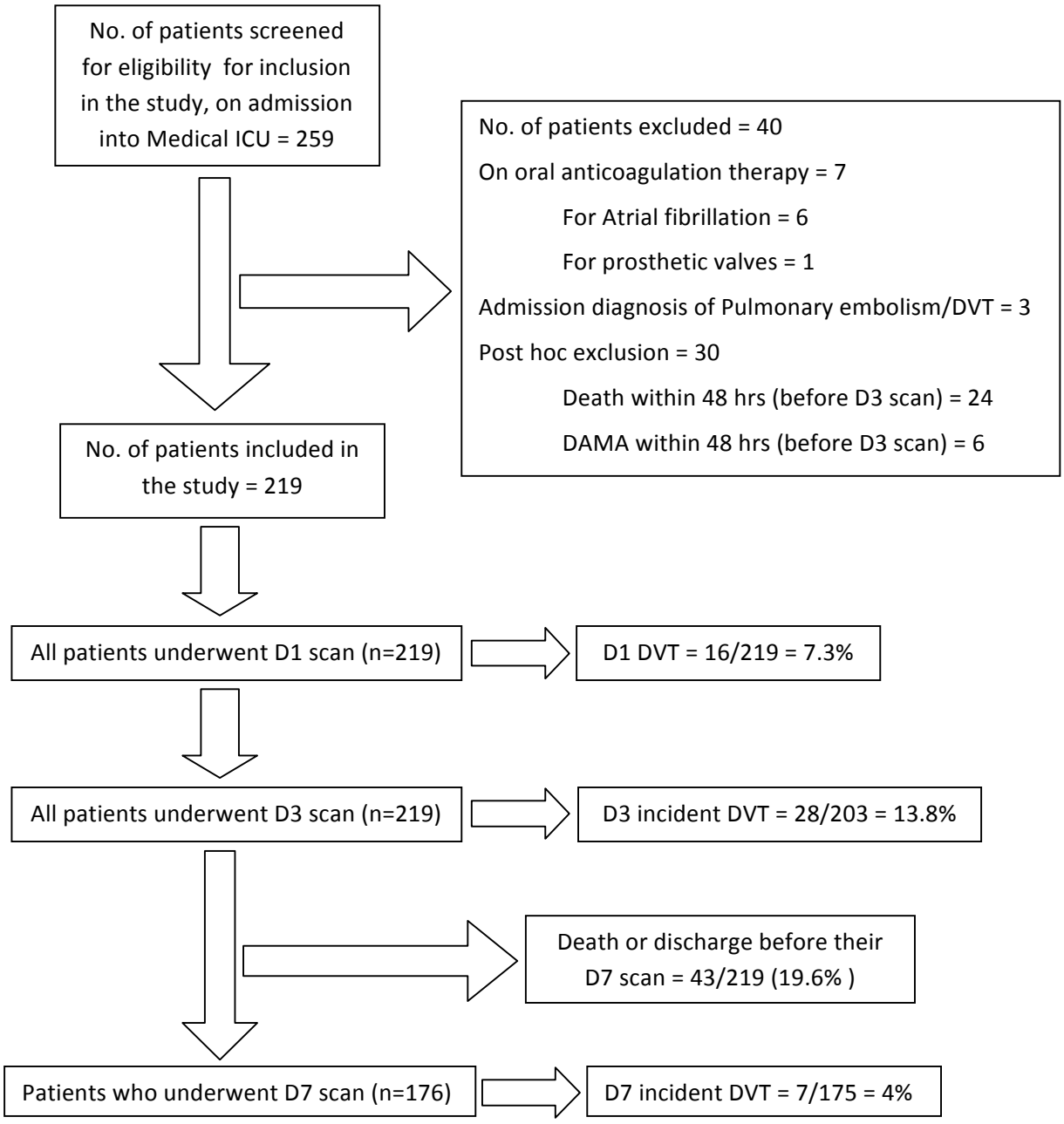


Table 1.a. Baseline characteristics in all patients studied - at admission into MICU

Characteristics of patients (n=219)	Frequency N (%)
Mean Age (yrs)	45.3 ± 17.5
Male gender	121 (55.3)
Past history	
Surgery (within 4 wks)	14 (6.4)
Trauma (within 4 wks)	4 (1.8)
Hospitalization (>3days)	39 (17.8)
Previous DVT	---
Pulmonary embolism	---
Central catheters	4 (1.8)
Dialysis ports	---
OCP intake (within 4 wks)	---
HRT (within 4 wks)	---
NSAID use	2 (0.9)
Rheumatic / autoimmune disease	15 (6.8)
Present history	
Congestive cardiac failure	9 (4.1)
Chronic liver failure	7 (3.2)
Chronic kidney disease	14 (6.4)
Malignancy	1 (0.5)
Pregnancy	---
Post partum	7 (3.2)
Immobilization (stroke/paresis)	7 (3.2)
Pacemaker Insertion*	4 (1.8)
Smoking	34 (15.5)
Alcohol	47 (21.5)
Aspirin	25 (11.4)
Clopidogrel	19 (8.7)
Vitamin K supplements	36 (16.4)
Other comorbidities	104 (47.5)
SOFA score at admission to ICU	**7.2 ± 4.2**
Symptoms suggestive of DVT	10 (4.7)
1) Erythema	1 (0.5)
2) Warmth	3 (1.4)
3) Swelling	5 (2.3)
4) Tenderness	1 (0.5)

*All patients who had undergone pacemaker insertion were on a temporary pacemaker.

Table 1.b. Baseline characteristics (contd.) – Interventions in the Medical ICU

Characteristics of patients (n=219)	Frequency, n (%)
Treatment in ICU	
Central Venous catheters	**154 (70.2)**
Internal Jugular	75 (48.7)
Right	71 (46.1)
Left	4 (2.6)
Subclavian	6 (3.8)
Right	5 (3.2)
Left	1 (0.6)
Femoral	73 (47.4)
Right	66 (42.9)
Left	7 (4.5)
Mean duration (days)	**7.1 ± 3.1**
Peripherally inserted central catheters	**3 (1.4)**
Right	2 (66.7)
Left	1 (33.3)
Mean duration (days)	**7.0 ± 2.6**
Dialysis ports	**17 (7.8)**
Jugular	4 (23.5)
Right	1 (5.9)
Left	3 (17.6)
Femoral	13 (76.5)
Right	6 (35.3)
Left	7 (41.2)
Mean duration (days)	**8.8 ± 4.9**
Mechanical ventilation	**164 (74.9)**
Mean duration (days)	**7.3 ± 5.0**
Sedatives	**134 (61.2)**
Mean duration (days)	**3.7 ± 2.6**
Vasopressors	**118 (53.9)**
Dopamine	4 (3.4)
Adrenaline	25 (21.2)
Noradrenaline	37 (31.4)
Dobutamine	2 (1.7)
Multiple	50 (42.4)
Mean duration (days)	**4.1 ± 2.8**
Transfusions	**29 (13.2)**
Packed cells	9 (31.0)
Whole blood	1 (3.8)
Platelets	4 (13.8)
Cryoprecipitate	3 (10.3)
Multiple	12 (41.4)

Table 1.c. Baseline characteristics - Thromboprophylaxis and Bleeding parameters

Characteristics of patients (n=219)	Frequency n (%)
Thromboprophylaxis	**219 (100)**
Pharmacological	122 (55.7)
Heparin	116 (95.1)
Enoxaparin	6 (4.9)
Adequate dosage	122 (100)
Mechanical	92 (42.0)
Both*	5 (2.3)
Laboratory investigations	
Mean PT	
D1 (n=189/219; 86.3%)	14.7 ± 9.0
D3 (n=206/219; 94.1%)	13.8 ± 5.0
D7 (n=169/219; 77.2%)	12.6 ± 3.7
Mean INR	
D1 (n=189/219=86.3%)	1.3 ± 0.8
D3 (n=206/219; 94.1%)	1.3 ± 0.5
D7 (n=169/219; 77.2%)	1.1 ± 0.3
Mean APTT	
D1 (n=187/219; 85.4%)	33.7 ± 13.7
D3 (n=205/219; 93.6%)	33.3 ± 12.7
D7 (n=167/219; 76.2%)	32.6 ± 11.4
Mean platelet counts	
D1 (n=216/219; 98.6%)	2,12,745 ± 1,42,259
D3 (n=218/219; 99.5%)	2,13,720 ± 2,33,085
D7 (n=175/219; 79.9%)	1,88,988 ± 1,19,562
Mean duration of ICU stay (days)	**7.2 ± 5.3**
Mean duration of hospitalization (days)	**14.6 ± 11.4**

*All patients who were on both, pharmacological & mechanical prophylaxis were on unfractionated heparin as part of the former.

PRIMARY OUTCOME: INCIDENCE OF DVT IN MEDICAL INTENSIVE CARE UNIT

The day 1 screening ultrasound, done on these 219 patients, picked up 16 patients with DVT (7.3%). All of these 219 patients underwent the day 3 follow up scan, which picked up an additional 28 patients with DVT amongst the 203 patients at risk (excluding the day 1 positive patients) (13.8%). Amongst these 219 patients, the day 7 scan was not done in 43 patients due to death or discharge within a week of ICU admission. Amongst the remaining 175 patients at risk, 7 patients had newly developed DVT on day 7 of ICU admission (4%). The incidence of DVT in our MICU was 17.2% (n=35/203), of which two thirds were catheter related (Table 2). It was interesting to note that three fourths of our DVTs were from the lower limb (all but one being femoral thrombi) (Table 3, Figures 2,3).

Table 2 – Primary Outcome : Incidence of DVT in Medical ICU (while on thromboprophylaxis)

Primary outcome	Incidence	95% CI
DVT at admission into ICU (D1)	16/219 = 7.3%	(3.85, 10.7)
Incident DVT (D3+D7)	**35/203 = 17.2%**	**(12.0, 22.3)**
Incident catheter related DVT	23/203 = 11.3%	(6.9, 15.6)
Incident non catheter related DVT	12/203 = 5.9%	(2.6, 9.1)
Total DVTs encountered in the ICU (D1+D3+D7)	**51/219 = 23.2%**	**(17.6, 28.8)**

Table 3 – Site of DVTs encountered in the study

Site	Incident DVTs (D3+D7) (n=35)	DVTs at admission (D1) (n=16)	Overall (D1+D3+D7) (n=51)	Catheter Related
Lower Limb	**25 (71.4%)**	14 (87.5%)	**39 (76.4%)**	25/39 (64.1%)
Femoral*	**24 (68.5%)***	14 (87.5%)	**38 (74.6%)**	25/38 (65.7%)
Popliteal	**1 (2.9%)**	-	**1 (1.9%)**	-
Upper Limb**	**8 (22.8%)**	2 (12.5%)	**10 (19.6%)**	8/10 (80%)
Multiple sites	**2 (5.8%)**	-	**2 (3.9%)**	-
Catheter Related	**23 (65.7%)**	10 (62.5%)	**33 (64.7%)**	

*2/24 were bilateral femoral DVTs

**All upper limb thrombi were contributed by jugular involvement. There were no axillary thromboses in our study.

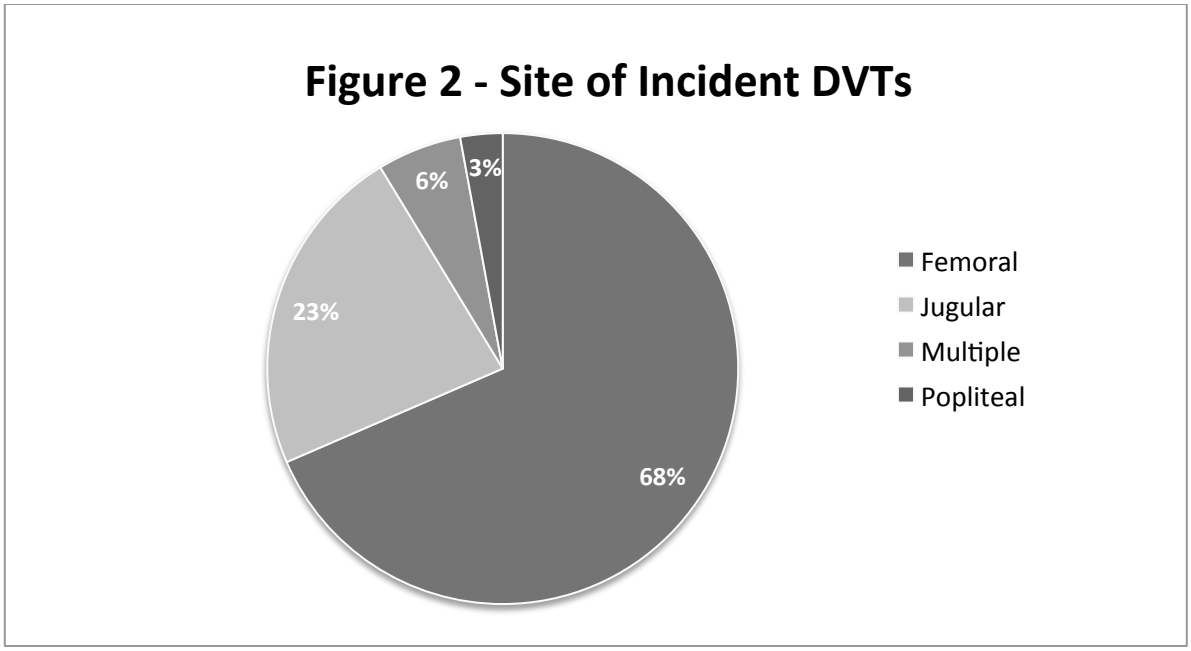


Figure 2 – Sites of Incident DVTs (Day 3 + Day 7) in the Medical ICU (n=35)

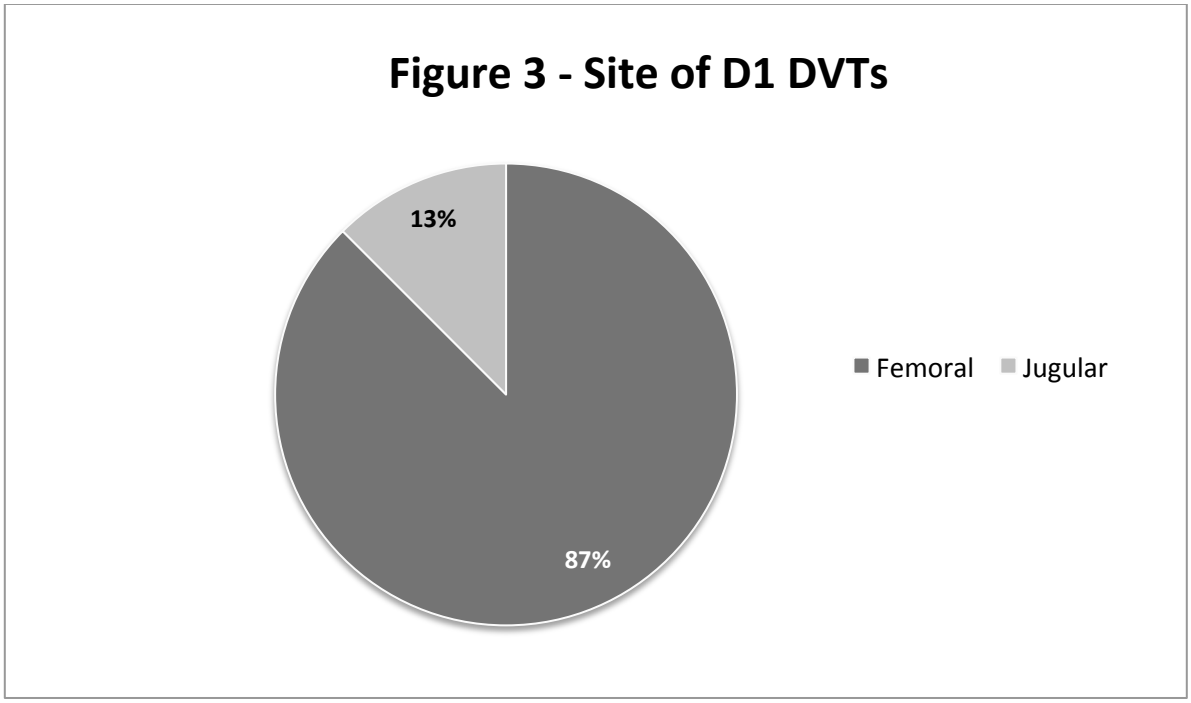


Figure 3 – Sites of Day 1 DVTs in the Medical ICU (n=16)

NATURAL COURSE OF THE DVTS ENCOUNTERED IN THE STUDY

Day 1 DVTs

Although the patients who had developed DVT on the day of admission into MICU were excluded from the calculation of incidence and from the risk factor analysis (as per protocol), they were followed up over one week with the day 3 and day 7 follow up scans. It was interesting to note that nearly half of them had resolved by 3 days (first follow up scan) and three-fourth by 7 days (Table 4, Figure 4).

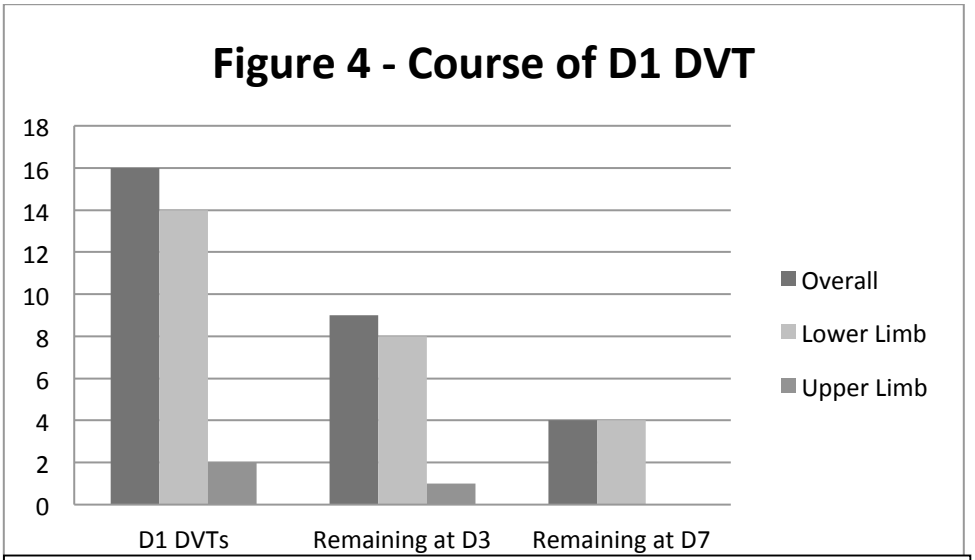


Figure 4 – Course of the day 1 DVTs (n=16). Overall (first bar), 42.9% resolve in 3 days and 71.4% resolve in 7 days. X axis shows the timeline, Y axis shows the numbers of DVTs.

Table 4 – Course of D1 DVTs in the Medical ICU

D1 DVTs	Resolution by D3	Overall resolution by D7
Lower Limb (n=14)	6 (42.9%)	10 (71.4%)
Upper Limb (n=2)	1 (50%)	2 (100%)
Catheter Related (n=10)	5 (50%)	8 (80%)
Overall (n=16)	7 (43.8%)	12 (75%)

Day 3 DVTs

All patients underwent 3 scans on Days 1, 3 and 7 of ICU admission. Therefore, all patients with D3 incident DVT had only one more follow up scan at day7. Further follow up scans beyond that period was considered not feasible. Observations were similar to those encountered with the day 1 DVTs. By the day 7 scan (first follow up scan), as with the day 1 DVTs, nearly half had spontaneously resolved (Table 5, Figure 5).

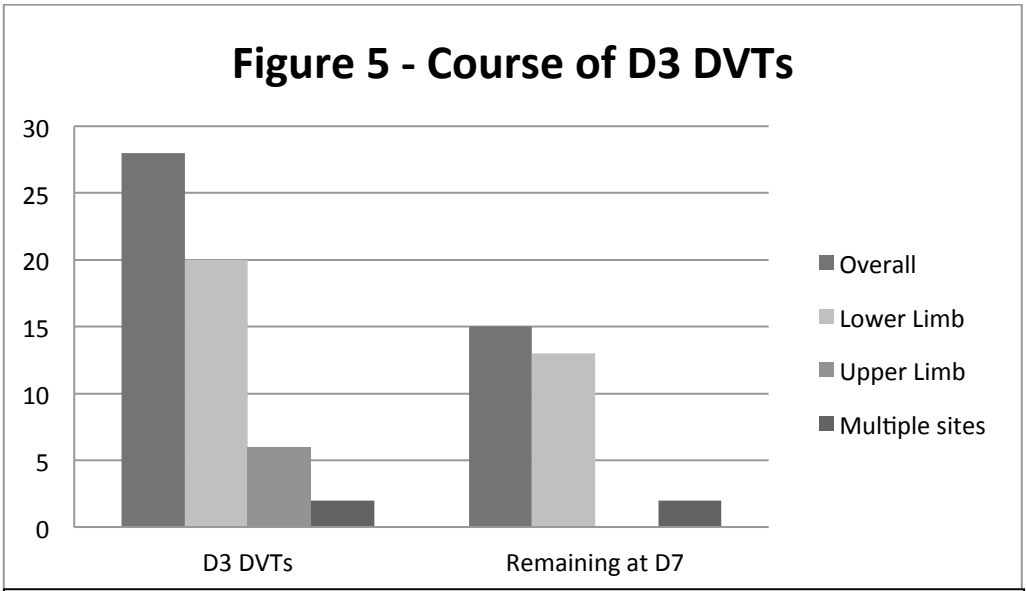


Figure 5 – Course of Day 3 Incident DVTs (n=35) encountered in the Medical ICU. Overall (first bar), 46.4% resolve over the subsequent 3 days. X axis shows the timeline and Y axis shows the numbers of DVTs.

Table 5 - Course of Incident D3 DVTs in the Medical ICU

D3 DVTs	Resolution by D7
Lower Limb (n=20)	7 (35%)
Upper Limb (n=6)	6 (100%)
Multiple sites (n=2)	-
Catheter Related (n=19)	9 (47.3%)
Overall (n=28)	13 (46.4%)

CATHETER RELATED DVTS

Nearly two thirds of all DVTs were catheter related (Table 3). Amongst the lower limb DVTs, two thirds were catheter related and amongst the upper limb, it was eighty percent (Table 6). Femoral DVTs attributed to nearly three fourths of catheter related DVTs. The natural course of the catheter related DVTs was similar to that of the non catheter related ones on serial follow up (Tables 7-9, Figures 6-10).

Table 6 - Sites of DVTs - Catheter related DVTs vs. Non catheter related DVTs

	Catheter Related DVTs (n=33)	Non Catheter Related DVTs (n=18)
Lower Limb	25 (75.8%)	14 (77.8%)
Upper Limb	8 (24.2%)	2 (11.1%)
Multiple sites	-	2 (11.1%)

Table 7 - Time of development of DVTs from the day of admission into the Medical ICU - Catheter Related vs. Non Catheter Related DVTs

DVT development	Catheter Related DVTs (n=33)	Non Catheter Related DVTs (n=18)
Day 1	10 (30.3%)	6 (33.3%)
Day 3	19 (57.6%)	9 (50%)
Day 7	4 (12.1%)	3 (16.7%)

Table 8 - Course of D1 DVTs - Catheter Related vs. Non Catheter Related

Day 1 DVT (n=16)	Catheter Related DVTs (n=10)	Non Catheter Related DVTs (n=6)
Resolution by D3	5 (50%)	2 (33.3%)
Resolution by D7	8 (80%)	4 (66.7%)

Table 9 - Course of D3 DVTs - Catheter Related vs. Non Catheter Related

Day 3 DVT (n=28)	Catheter Related DVTs (n=19)	Non Catheter Related DVTs (n=9)
Resolution by D7	9 (47.3%)	4 (44.4%)

Figure 6 - Day 1 DVTs

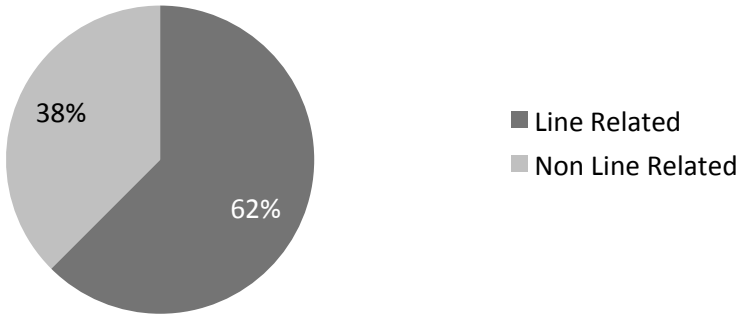


Figure 6 – Catheter Related vs. Non Catheter related - Amongst the Day 1 DVTs (n=16), 62% were catheter related ones.

Figure 7 - Day 3 DVTs

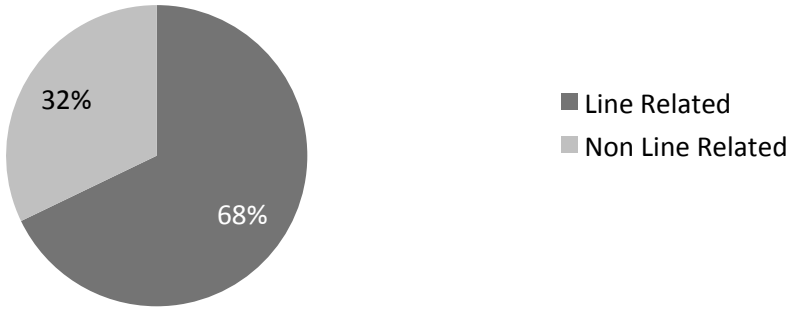


Figure 7 – Catheter Related vs. Non Catheter Related - Amongst the Day 3 DVTs (n=35), 68% were catheter related ones.

Figure 8 - Day 7 DVTs

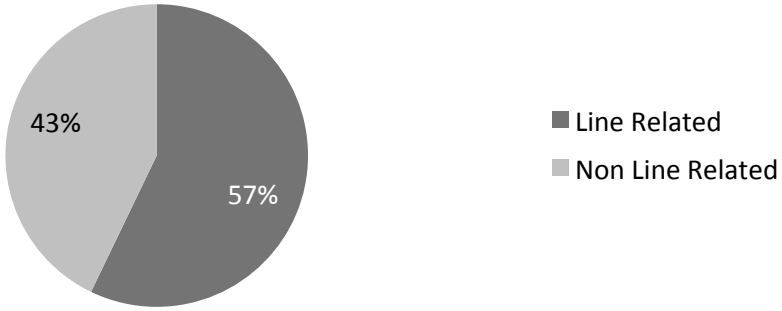


Figure 8 – Catheter Related vs. Non Catheter Related - Amongst the Day 7 DVTs (n=7), 57% were catheter related ones.

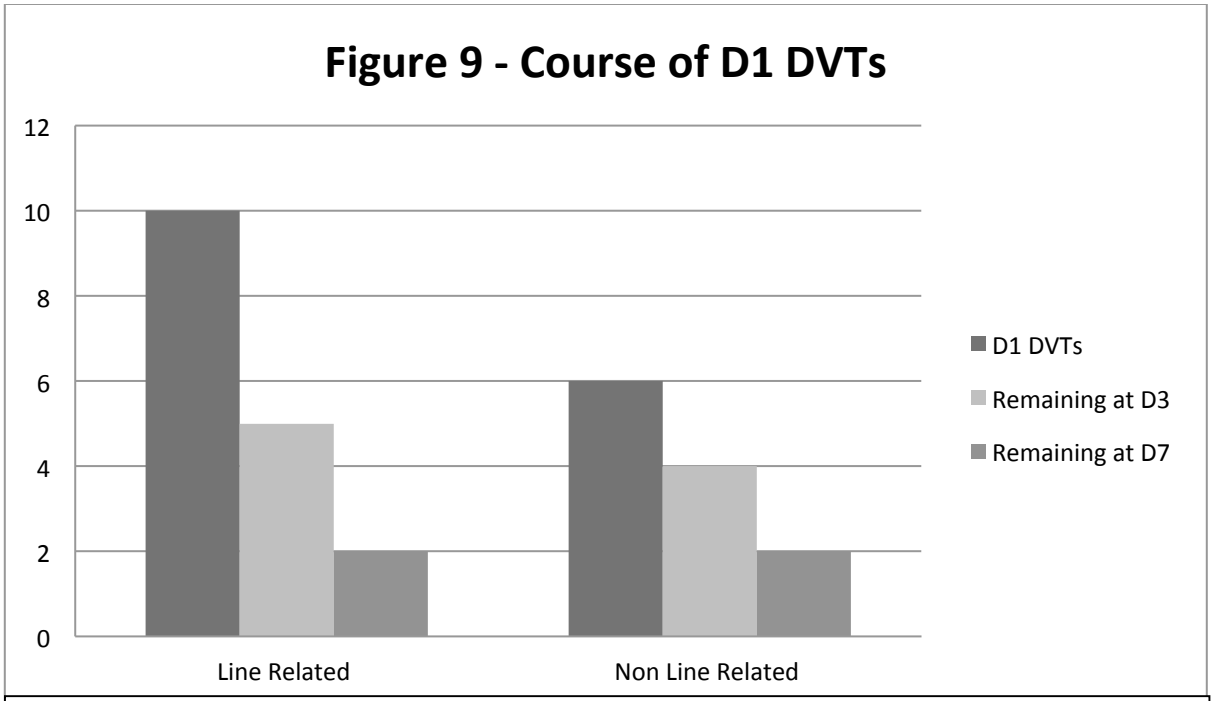


Figure 9 – Course of the Catheter Related (n=10) vs. Non Catheter Related (n=6) Day 1 DVTs. X axis shows the catheter related vs. non catheter related DVTs with the time catheter ; Y axis shows the numbers of DVTs.

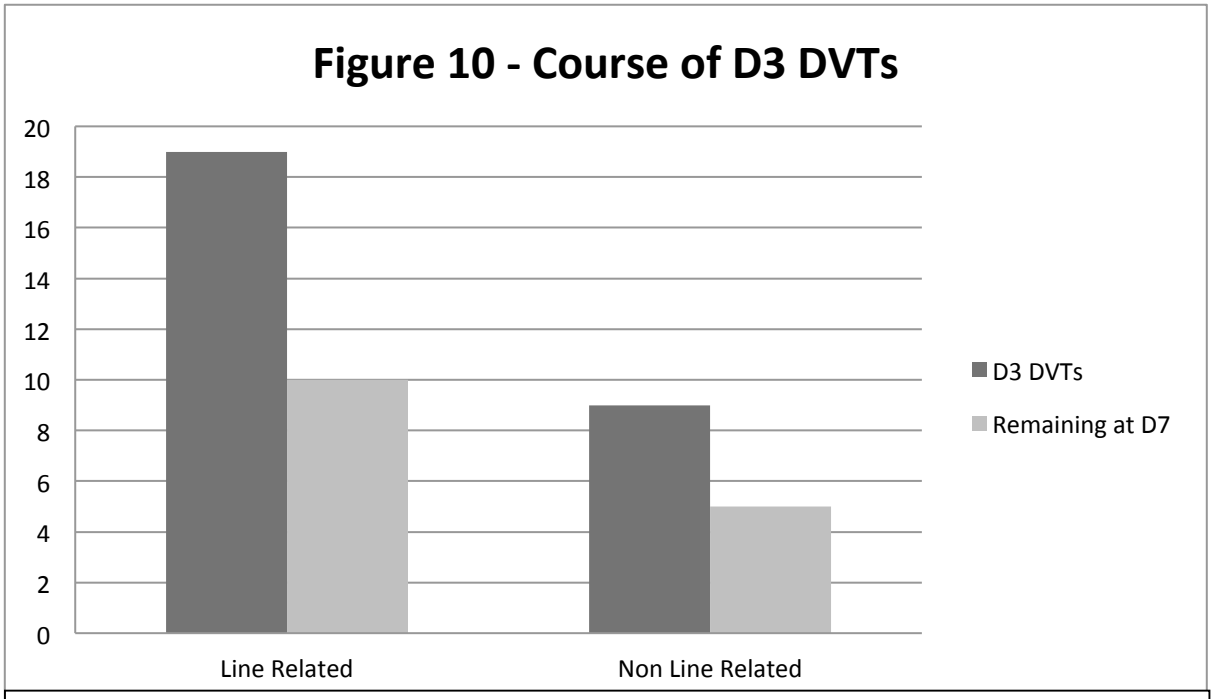


Figure 10 – Course of the Catheter Related (n=19) vs. Non Catheter Related (n=9) Day 3 DVTs. X axis shows the catheter related vs. non catheter related DVTs with the time catheter ; Y axis shows the numbers of DVTs.

TYPE OF THROMBI ENCOUNTERED

The thrombi encountered in our study were characterized based on their sonological characteristics into one of the following three types:

1) Complete thrombosis* was characterized by complete lack of compressibility of the vein or visualization of the thrombus nearly causing total luminal occlusion or absence of flow in the colour flow imaging.
2) Partial thrombosis** was characterized by partial luminal obstruction as evidenced by the vein being partially compressible or visualization of a thrombus partly occluding the lumen or colour flow imaging showing partial flow across the lumen.
3) Small catheter related thrombus*** was characterized by the presence of echogenic small thrombus around the catheter precluding complete compressibility.

Seventeen thrombi were encountered amongst the sixteen patients, in whom day 1 DVT was identified (one patient had bilateral femoral DVT). It was surprising that one third of the DVTs encountered on the day of admission into MICU were attributed to complete thrombosis. However, all the jugular thrombi were only small catheter related ones (Table 10)

Amongst the 28 patients, in whom day 3 incident DVT was identified, 30 thrombi were encountered (Table 11). Two patients had thrombosis at multiple sites, one at femoral (complete) and popliteal (partial) and the other at femoral (small catheter related) and jugular (complete). Nearly half were small catheter related ones while the remaining were contributed equally by complete and partial thrombi. Almost all the jugular thrombi were small catheter related ones. A similar trend was observed among the day 7 DVTs and the overall DVTs encountered in the study (Tables 12, 13).

Table 10 – Type of Thrombus encountered among the Day 1 DVTs

Day 1 DVTs (n=17)	Complete thrombosis*	Partial thrombosis **	Small catheter related thrombus***	Total
Jugular	-	-	2 (100%)	2 (11.8%)
Femoral	6 (40%)	1 (6.7%)	8 (53.3%)	15 (88.2%)
Total	6 (35.3%)	1 (5.9%)	10 (58.8%)	17

Table 11 – Type of Thrombus encountered among the Day 3 DVTs

Day 3 DVTs (n=30)	Complete thrombosis*	Partial thrombosis **	Small catheter related thrombus***	Total
Jugular	1 (12.5%)	-	7 (87.5%)	8 (26.7%)
Femoral	7 (35%)	7 (35%)	6 (30%)	20 (66.7%)
Popliteal	-	2 (100%)	-	2 (6.6%)
Total	8 (26.7%)	9 (30%)	13 (43.3%)	30

Table 12 – Type of Thrombus encountered among the Day 7 DVTs

Day 7 DVTs (n=7)	Complete thrombosis*	Partial thrombosis **	Small catheter related thrombus***	Total
Jugular	-	-	2 (100%)	2 (28.6%)
Femoral	2 (40%)	2 (40%)	1 (20%)	5 (71.4%)
Total	2 (28.6%)	2 (28.6%)	3 (42.8%)	7

Table 13 – Type of Thrombus encountered among the overall DVTs seen in our study

All thrombi encountered	Complete thrombosis	Partial thrombosis	Small catheter related thrombus***	Total
Jugular	1 (8%)	-	11 (92%)	12 (22.2%)
Femoral	15 (37.5%)	10 (25%)	15 (37.5%)	40 (74.1%)
Popliteal	-	2 (100%)	-	2 (3.7%)
Total	16 (29.6%)	12 (22.2%)	26 (48.2%)	54

SECONDARY OUTCOMES: DEATH, DISCHARGE & DURATION OF HOSPITAL STAY

The in-hospital mortality rate in the entire study group was 24.7% (n=54/219). Nearly three fourths of the in-hospital deaths occurred in the intensive care unit (n=42, 77.8%). Sudden deaths contributed to 16.7% (n=9) of the overall mortality in the hospital. A small percentage of patients were discharged against medical advice (n=14/219, 8.7%). The mean duration of ICU stay was 1 week and that of hospitalization was 2 weeks.

The results of a positive scan were conveyed to the treating physician, who decided further course of management, to their discretion. Most of them were observed till discharge, for clinical evidence of DVT or its proximal propagation, with only 3 patients (8.57%) (amongst the 35 patients newly diagnosed with DVT in the medical ICU), being discharged with a diagnosis of DVT, having been initiated on oral anticoagulation therapy. It was presumed that the DVT detected in the remaining patients had spontaneously resolved. This was however, not confirmed, as serial scans following the day 7 scan was beyond the scope of the study due to feasibility constraints. All the three patients had been identified earlier during the study, with two of them being detected on day 3 and one on day 7. One of them had bilateral femoral thrombi, while the two others had jugular involvement in addition to femoral thrombi.

INCIDENT DVT VS. NON DVT

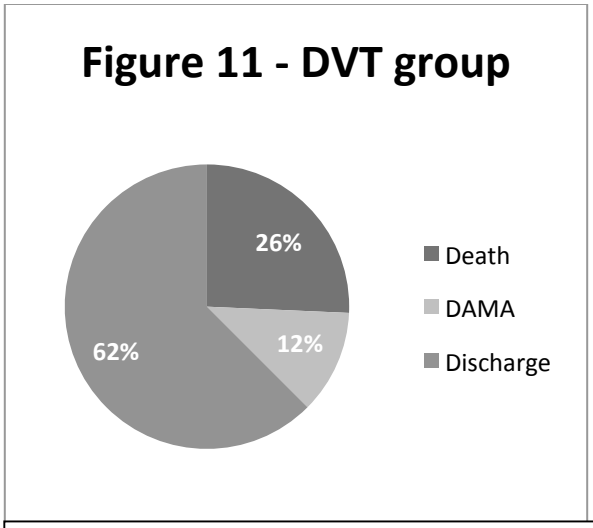
A comparison between the secondary outcomes observed in the Incident DVT group (n=35) and the non DVT group (n=168) (Figures 11-14) showed that the mean duration of hospital stay was significantly higher in the DVT group (Table 14, Figures 15). The mean

duration of ICU stay at the development of DVT was 3.8 ± 1.6 days and the same for hospital stay was 7.2 ± 6.7 days. This signifies that the high risk period for DVT development was around the third day of ICU stay and around a week of hospital stay. The proportion of sudden deaths was more in the DVT group, however this observation was not statistically significant. There were no cases of confirmed pulmonary embolism in our study. However, amongst the nine sudden deaths, there was only one case of clinically suspected pulmonary embolism. This occurred in a patient with femoral and jugular thromboses.

Table 14 – Comparison between the Secondary Outcomes observed in the Incident DVT group vs. Non DVT group

Total (n=203)	Incident DVT group (n=35)	Non DVT group (n=168)	P value
Death			
In hospital	9 (25.7)	40 (23.8)	0.81
In ICU	6 (17.6)	31 (18.7)	0.85
Death – all cause			
Sudden death	3 (33.3)	6 (15)	0.19
Confirmed / probable PE	---	---	
Other causes	6 (66.7)	34 (85)	0.675
Discharge against medical advice	4 (11.8)	14 (8.4)	0.55
Discharge diagnosis of DVT*	3 (8.6)	---	<0.001
Mean duration of ICU stay (days)	8.9 ± 6.1	6.96 ± 5.3	0.056
Median & IQR	7 (4.75, 12.25)	5 (4,9)	
Mean duration of hospital stay (days)	23.1 ± 18.3	12.97 ± 8.5	<0.001
Median & IQR	20.5 (10,25)	10.5 (7, 16)	
Mean duration of ICU stay at development of DVT (days)	3.8 ± 1.6		
Mean duration of hospitalization at development of DVT (days)	7.2 ± 6.7		

*2 patients had non catheter related DVT and one of them had a catheter related DVT
IQR- Interquartile range



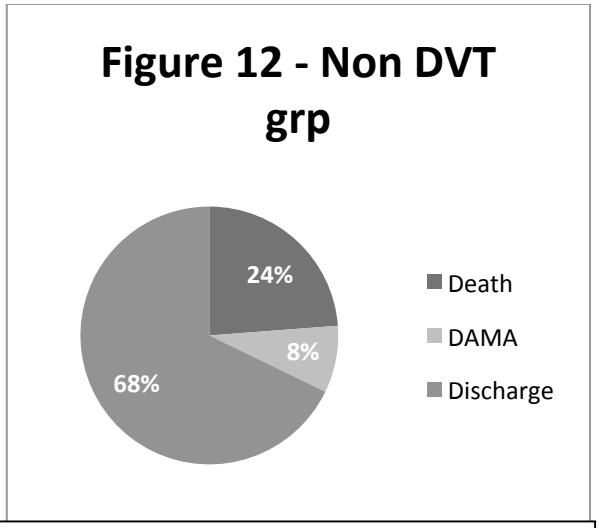
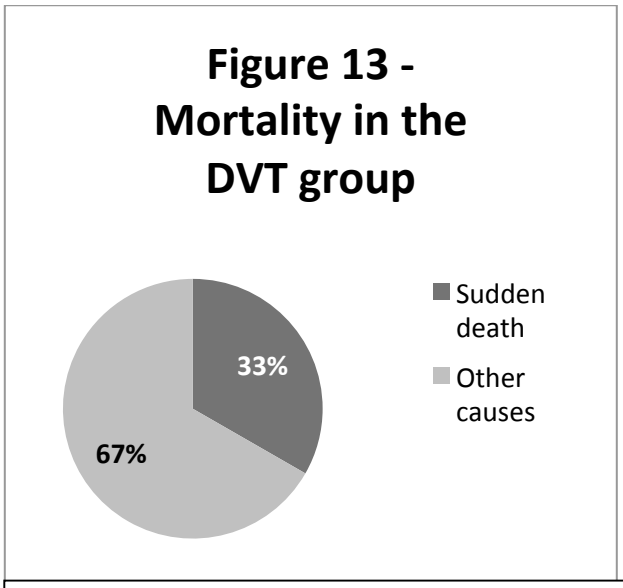


Figure 11 – Secondary Outcomes in the Incident DVT (n=35) group.
Figure 12 – Secondary Outcomes in the Non DVT (n=168) group.
The secondary outcomes were largely similar in both the groups.



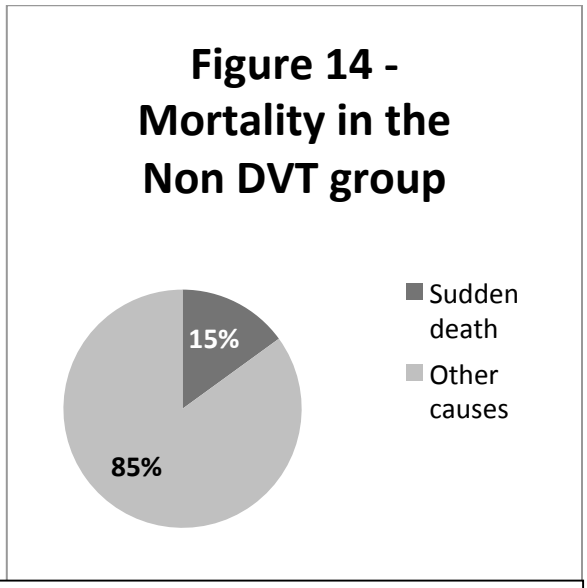


Figure 13 – Mortality in the Incident DVT (n=35) group.
Figure 14 – Mortality in the Non DVT (n=168) group.
Although, the proportion of sudden deaths was higher in the incident DVT group (33% vs. 15%), this difference was not statistically significant (p=0.19).

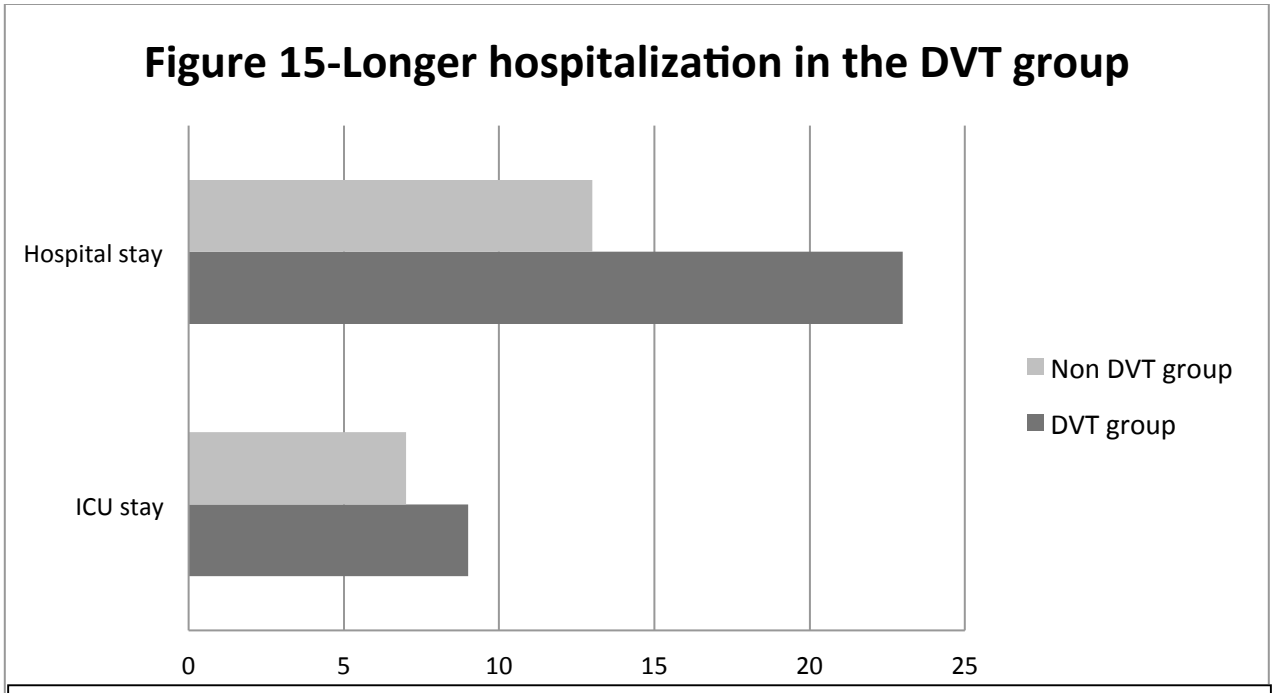
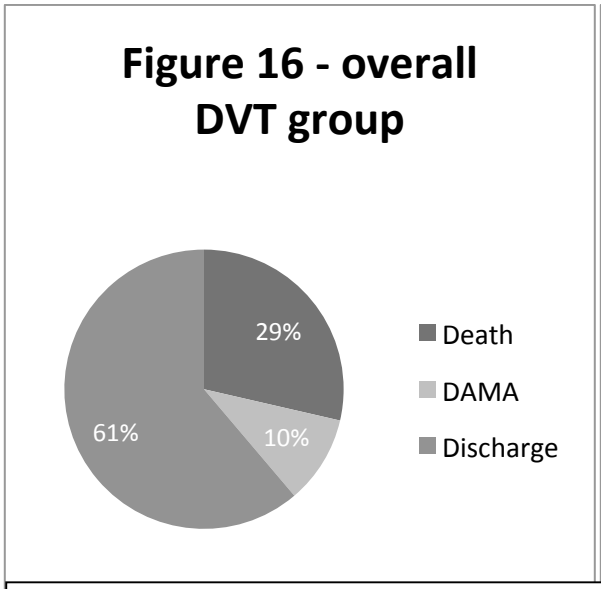


Figure 15 – Duration of ICU stay and hospital stay – Incident DVT group (n=35) vs. Non DVT group (n=168). Although both were longer in the DVT group, the duration of hospital stay was significantly longer in the former ($p<0.001$) with a difference of 10 days between the median duration of hospitalization between the 2 groups (20.5 vs. 10.5 days)

Table 15 – Comparison between the Secondary Outcomes observed in the Overall DVT group vs. Non DVT group

Total (n=219)	Overall DVT group (n=51)	Non DVT group (n=168)	P Value
Death			
In hospital (total)	14 (28.6)	40 (23.8)	0.59
In ICU	11 (22.4)	31 (18.7)	0.62
Death – all cause			
Sudden death	3 (21.4)	6 (15)	0.46
Confirmed / probable PE	---	---	
Other causes	11 (78.6)	34 (85)	0.83
Discharge against medical advice	5 (10.2)	14 (8.4)	0.74
Discharge diagnosis of DVT	3 (5.9)	---	<0.002
Mean duration of ICU stay (days)	7.9 ± 5.6	6.96 ± 5.3	0.274
Median & IQR	6 (4,11)	5 (4,9)	
Mean duration of hospital stay (days)	20.1 ± 17.0	12.97 ± 8.5	<0.001
Median & IQR	19 (9,23.5)	10.5 (7,16)	
Mean duration of ICU stay at development of DVT (days)	2.9 ± 1.9		
Mean duration of hospitalization at development of DVT (days)	6.1 ± 6.5		

IQR=interquartile range



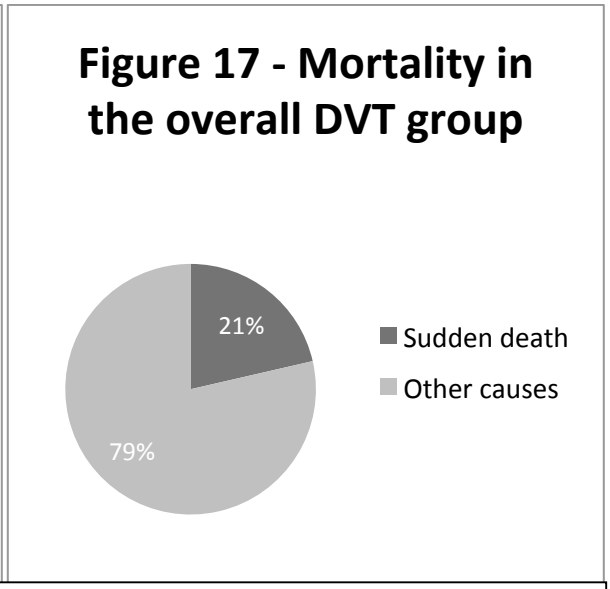


Figure 16 – Secondary Outcomes in the Overall DVT (n=51) group.
Figure 17 – Mortality in the Overall DVT (n=51) group.
On comparing with figures 12 & 14, the secondary outcomes appeared largely similar between the 2 groups.

SECONDARY OUTCOMES IN THE NON CATHETER RELATED DVT GROUP

Only one thirds of the incident DVTs were non-catheter related in our study. Catheter related DVTs were thought to be related to the presence of a central venous catheter and hence its natural course was thought to be dependent on the life of the catheter, with most of them being transient and resolving spontaneously. In contrast, the non-catheter related DVTs were thought to be more reflective of the dynamic changes in the coagulation system in the critically ill, which favoured their development. Therefore, it was interesting to pitch the secondary outcomes seen in the incident non-catheter related DVT group against the non DVT group (Table 16). The duration of hospital stay was longer in the former, similar to the observations made earlier.

Table 16 – Comparison between the Secondary outcomes observed in the Non catheter related DVT group vs. Non DVT group

Total (n=180)	Non catheter related DVT (n=12)	Non DVT group (n=168)	P value
Death			
In hospital	3 (25)	40 (24.1)	0.92
In ICU	2 (16.7)	31 (18.7)	0.87
Death – all cause			
Sudden death	1 (33.3)	6 (15)	0.41
Confirmed / probable PE	---	---	
Other causes	2 (66.7)	34 (85)	0.76
Discharge against medical advice	1 (8)	14 (8.4)	1.00
Discharge diagnosis of DVT	2 (16.7)	---	<0.001
Mean duration of ICU stay (days)	9.25 ± 8.24	6.96 ± 5.3	0.167
Median & IQR	6.5 (3.25, 14.75)	5 (4,9)	
Mean duration of hospital stay (days)	29.17 ± 15.32	12.97 ± 8.5	<0.001
Median & IQR	25 (22, 36)	10.5 (7,16)	
Mean duration of ICU stay at development of DVT (days)	4 ± 1.81 3 (3, 6)		
Mean duration of hospitalization at development of DVT (days)	9.33 ± 6.21 7.5 (4, 13)		

IQR=interquartile range

NON CATHETER RELATED DVT GROUP VS. CATHETER RELATED DVT GROUP

The secondary outcomes of the incident DVT group were compared between the non catheter related and the catheter related ones, in order to appreciate the differences with respect to their clinical outcomes (Table 17). There was no statistically significant difference between their outcomes. This was thought to be attributable to the small number of events in both the groups. However, the mean duration of hospital stay and the mean duration of hospitalization at the time of development of DVT appeared to be longer in the non catheter related DVT group. Although their p values were not statistically significant, they were less than 20% and hence it was thought that the difference might have been statistically significant had the event rate been higher.

Table 17 – Comparison between the Secondary Outcomes observed in the Non catheter related DVT group vs. catheter related DVT group

Total (n=35)	Non catheter related DVT (n=12)	Catheter related incident DVT (n=23)	P value
Death			
In hospital	3 (25)	6 (26.1)	0.94
In ICU	2 (16.7)	4 (17.4)	0.95
Death – all cause			
Sudden death	1 (33.3)	2 (33.3)	0.97
Confirmed / probable PE			
Other causes	2 (66.7)	4 (66.7)	0.95
Discharge against medical advice	1 (8)	3 (13.04)	0.67
Discharge diagnosis of DVT*	2 (16.7)	1 (4.35)	0.21
Mean duration of ICU stay (days)	9.25 ± 8.24	8.77 ± 4.67	0.826
Median & IQR	6.5 (3.25, 14.75)	7.5 (5,12.25)	
Mean duration of hospital stay (days)	29.17 ± 15.32	19.77 ± 19.32	0.154
Median & IQR	25 (22, 36)	18.5 (9.5, 21)	
Mean duration of ICU stay at development of DVT (days)	4 ± 1.81	3.70 ± 1.55	0.61
	3 (3, 6)	3 (3, 3)	
Mean duration of hospitalization at development of DVT (days)	9.33 ± 6.21	6.13 ± 6.81	0.183
	7.5 (4, 13)	4 (3, 7)	

IQR=interquartile range

RISK FACTOR ANALYSIS

RISK FACTORS FOR DEVELOPMENT OF DVT IN THE MEDICAL ICU

. One of the objectives of the study was to determine the risk factors unique to development of DVT in the critically ill medical patients. As the risk factors would have to be indigenous to the ICU setting (implying adequate exposure to the ICU risk factors which would in turn require a minimum period of ICU stay of atleast 48 hours), the day 1 DVTs were excluded from the risk factor analysis. Bivariate analysis (Table 18) revealed the following to be the statistically significant risk factors for development of DVT in the Medical ICU:

1) Central Venous Catheter, RR=15.67 (2.11, 111.85)
2) Age more than 40 years, RR=2.43 (1.16, 5.08)
3) Vasopressors, RR=2.19 (1.11, 4.34)
4) Day3 PT ($p=0.003$) & INR ($p<0.001$)

Age was directly related to the development of DVT. Gender was not significant although, the males seemed to be at a lesser risk for developing DVT (0.76, (0.42, 1.4)). Amongst the exposure risk factors, there was no statistically significant difference between the two groups. Although, the insertion of a pacemaker appeared to be a risk factor with a relative risk of 1.96 (0.38, 10.0), it was not statistically significant. All the effect modifiers (aspirin, clopidogrel, vitamin K) appeared to be protective against the development of DVT, although, there was no statistical significance. Most of the DVTs encountered in the MICU were asymptomatic with only 2 patients exhibiting clinical features suggestive of DVT (erythema and swelling).

The presence of central venous catheters appeared to confer the highest risk. Amongst the central venous catheters, it was seen that a femoral catheter, on its own, conferred a risk of 2.35 (1.30, 4.25). Similar observations were also made amongst the dialysis ports, wherein, a femoral port conferred a risk of 2.65 (1.25, 5.59), although the former per se was not a statistically significant risk factor. The duration of central venous catheters was also significantly associated with the development of DVT. Amongst the vasopressors, which had conferred a risk of 2.19 (1.11, 4.34), the use of multiple vasopressors conferred the highest risk (2.13, (1.77, 3.88)). Although the platelet transfusions appeared to confer a risk of 4.0 (0.66, 23.98), this was not statistically significant. Amongst the bleeding parameters, PT and INR on day 3 were found to be significant factors affecting the development of DVT.

Table 18 – Bivariate Analysis – Risk factors associated with development of DVT in MICU

Risk factors (n=203)	DVT group (n=35) n (%)	Non DVT group (n=168) n (%)	Relative Risk	95% CI	P value
Mean Age (yrs)	51.0 ± 14.7	43.9 ± 17.8		1.35, 12.71	0.016
Age >40 yrs	27 (23.0)	91 (77.0)	**2.43**	1.16, 5.08	0.020
Age <40 yrs	8 (9.0)	77 (91.0)			
Male gender (n=112)	17 (15.2)	95 (84.8)	0.767	0.42, 1.40	0.498
Female gender (n=91)	18 (19.78)	73 (80.22)			
Past history					
Surgery (within 4 wks) (n=13)	2 (15.38)	11 (84.62)	0.885	0.24, 3.29	0.844
Trauma (within 4 wks) (n=3)	---	3 (100)			
Hospitalization (>3days) (n=35)	5 (14.29)	30 (85.71)	0.80	0.33, 1.92	0.792
Central catheters (n=4)	2 (50)	2 (50)	1.00		
NSAID use (n=2)	---	2 (100)			
Rheumatic / autoimmune (n=11)	1 (9.09)	10 (90.91)	0.51	0.08, 3.41	0.744
Present history					
Congestive cardiac failure(n=9)	1 (11.11)	8 (88.89)	0.634	0.09, 4.13	0.963
Chronic liver failure (n=7)	1 (14.29)	6 (85.71)	0.823	0.13, 5.19	0.765
Chronic kidney disease (n=13)	1 (7.69)	12 (92.31)	0.429	0.06, 2.90	0.573
Malignancy (n=1)	---	1 (100)			
Post partum (n=7)	1 (14.29)	6 (85.71)	0.824	0.13, 5.19	0.765
Immobilization (n=6)	1 (16.67)	5 (83.33)	0.965	0.15, 5.93	0.609
Pacemaker Insertion (n=3)	1 (33.33)	2 (66.67)	1.96	0.38, 10.0	0.978
Smoking (n=31)	5 (16.13)	26 (83.87)	0.925	0.39, 2.20	0.936
Alcohol (n=46)	6 (13.04)	40 (86.96)	0.706	0.31, 1.60	0.525
Aspirin (n=23)	2 (8.7)	21 (91.3)	0.474	0.12, 1.85	0.390
Clopidogrel (n=18)	3 (16.67)	15 (83.33)	0.964	0.33, 2.84	0.795
Vitamin K supplements (n=32)	4 (12.5)	28 (87.5)	0.689	0.26, 1.80	0.604
Other comorbidities (n=93)	20 (21.51)	73 (78.49)	1.58	0.85, 2.90	0.196
SOFA score at admission to ICU	**7.7 ± 3.4**	**6.9 ± 4.3**		**-0.68, 2.37**	**0.277**

Symptoms of DVT (n=6)	2 (33.3)	4 (66.7)	1.98	0.61, 6.43	0.609
Treatment in ICU					
Central Venous	34 (24.46)	105 (75.54)	**15.65**	2.11, 111.85	<0.001
catheters(n=139)	15 (21.13)	56 (78.87)	1.39	0.76, 2.55	0.378
Internal Jugular	13 (19.1)	55 (80.9)	1.17	0.63, 2.18	0.760
Right	2 (66.67)	1 (33.33)	4.04	1.71, 9.53	0.07
Left	1(20)	4 (80)	1.16	0.20, 6.90	0.66
Subclavian	---	4 (3.8)			
Right	1 (2.9)	---			
Left	18 (28.57)	45 (71.43)	2.35	1.30, 4.25	0.007
Femoral	18 (52.9)	42 (40.0)	2.52	1.39, 4.55	0.003
Right	---	3 (2.9)			
Left	8.2 ± 3.3	6.96 ± 2.97		0.019, 2.41	0.047
Mean duration (days)					
	1 (33.33)	2 (66.67)	1.96	0.38, 10.0	0.978
PIC catheters* (n=3)	1 (100)	1 (50)			
Right	---	1 (50)			
Left	10.0	5.5 ± 0.7		-6.5, 15.5	0.121
Mean duration (days)					
	5 (35.71)	9 (64.29)	2.25	1.03, 4.88	0.126
Dialysis ports (n=14)	---	2 (22.2)			
Jugular		---			
Right		2 (22.2)			
Left	5 (41.67)	7 (58.33)	2.65	1.25, 5.59	0.05
Femoral	1 (20)	4 (80)	1.16	0.20, 6.90	0.66
Right	4 (57.14)	3 (42.86)	3.61	1.76, 7.41	0.02
Left	9.8 ± 4.1	8.4 ± 4.9		-4.27, 6.98	0.609
Mean duration (days)					
	25 (16.23)	129 (83.77)	0.795	0.41, 1.54	0.647
Mechanical ventilation(n=154)	8.0 ± 4.9	7.3 ± 5.2		-1.49, 2.93	0.520
Mean duration (days)					
	19 (15.08)	107 (84.92)	0.725	0.40, 1.32	0.394
Sedatives (n=126)	4.2 ± 2.2	3.6 ± 2.7		-0.79, 1.84	0.433
Mean duration (days)					
	25 (23.15)	83 (76.85)	**2.19**	1.11, 4.34	0.028
Vasopressors (n=108)	1 (33.33)	2 (66.67)	1.96	0.38, 10.0	0.978
Dopamine	5 (20.83)	19 (79.17)	1.24	0.53, 2.90	0.834
Adrenaline	6 (17.14)	29 (82.86)	0.99	0.44, 2.21	0.818
Noradrenaline	---	2 (2.4)			
Dobutamine	13 (29.55)	31 (70.45)	2.13	1.17, 3.88	0.03
Multiple	4.0 ± 2.1	4.0 ± 2.9		-1.28, 1.21	0.954
Mean duration (days)					
	5 (17.86)	23 (82.14)	1.04	0.44, 2.46	0.859

Transfusions (n=28)	1 (12.5)	7 (87.5)	0.716	0.11, 4.60	0.908
Packed cells	1 (20)	---			
Whole blood	1 (25)	3 (75)	4.00	0.66, 23.98	0.636
Platelets	---	3 (13)			
Cryoprecipitate	2 (16.67)	10 (83.33)	0.96	0.26, 3.55	0.734
Multiple					
Laboratory investigations					
Mean PT					
D1	14.2 ± 3.1	14.0 ± 6.0		-1.85, 2.25	0.88
D3	16.1 ± 9.4	13.3 ± 3.6		0.94, 4.65	0.003
D7	12.7 ± 2.2	12.6 ± 4.1		-1.30, 1.50	0.888
Mean INR					
D1	1.3 ± 0.3	1.3 ± 0.5			
D3	1.5 ± 0.9	1.2 ± 0.3		0.13, 0.468	<0.001
D7	1.2 ± 0.2	1.1 ± 0.3		-0.04, 0.20	0.06
Mean APTT					
D1	33.4 ± 7.9	32.9 ± 12.7		-3.90, 4.90	0.823
D3	37.3 ± 14.8	32.8 ± 12.7		-0.29, 9.29	0.065
D7	32.97 ± 9.6	32.0 ± 10.6		-2.85, 4.79	0.617
Mean platelet counts					
D1 (mean, SD)	2.49L ± 1.76L	2.14L ± 1.35L		-0.17, 0.87	0.191
(Median, IQR)	2.07L(1.2,3.45)	2.1L(1.04,3.07)			
D3 (mean, SD)	2.01L ± 1.56L	2.25L ± 2.53L		-1.11, 0.64	0.599
(Median, IQR)	1.75L(0.63,2.8)	1.89L(0.8,2.86)			
D7 (mean, SD)	1.87L ± 1.17L	1.91L ± 1.23L		-0.48, 0.40	0.853
(Median, IQR)	1.58L(1.03,2.67)	1.83L(0.93,2.6)			
Thromboprophylaxis	35 (17.2)	168 (82.8)			
Pharmacological	19 (16.67)	95 (83.33)	0.927	0.51, 1.70	0.953
Heparin	18 (16.7)	90 (83.3)	0.93	0.51, 1.70	0.964
Enoxaparin	1 (16.67)	5 (83.3)	0.965	0.16, 5.93	0.609
Adequate dosage	19 (100)	95 (100)			
Mechanical	16 (19.05)	68 (80.95)	1.19	0.65, 2.18	0.701
Both	---	5 (3.0)			

No comparisons were made as one of the arms either had complete absence of the risk factor, or the occurrence was equal in both the arms.

IQR=interquartile range, SD=standard deviation, PIC=peripherally inserted central catheters.

PT and APTT have been given in seconds and platelets in lakhs.

INDEPENDENT RISK FACTORS FOR DEVELOPMENT OF DVT IN THE MEDICAL ICU

Multivariate analysis included the risk factors which were significantly associated with the development of DVT. In addition to age, central venous catheters, vasopressors and day 3 INR; SOFA score was also included in the analysis to adjust for severity of comorbidities. Central venous catheters emerged as the sole independent risk factor (Table 19). Age and day 3 INR were also found to confer additional risk in the development of DVT, but were not statistically significant. This model was found to predict 20% of the variability (based on the R square value) and was also found to be of adequate fit (Hosmer Lemeshow test value >0.05).

Table 19 - Multivariate Analysis - Risk factors for Development of DVT in MICU – Model 1

S.No.	Risk Factors	Relative Risk	95% CI	P Value
1.	*Central Venous Catheters*	15.97	1.88, 135.84	0.01
2.	Day 3 INR	2.16	0.87, 5.34	0.09
3.	Age > 40 yrs	2.05	0.79, 5.34	0.14
4.	Vasopressors	1.01	0.36, 2.88	0.93
5.	SOFA	0.95	0.85, 1.06	0.34

Nagelkerke R Square = 0.209, Hosmer-Lemeshow test value = 0.347 (good fit)

Similar modeling was done with the substitution of day 3 PT instead of INR, which also yielded similar results (Table 20). This model was also found to be of adequate fit.

Table 20 - Multivariate Analysis - Risk factors for Development of DVT in MICU – Model 2

S.No.	Risk Factors	Relative Risk	95% CI	P Value
1.	*Central Venous Catheters*	16.13	1.89, 137.25	0.01
2.	Day 3 PT	1.07	0.98, 1.16	0.09
3.	Age > 40 yrs	2.03	0.78, 5.29	0.15
4.	Vasopressors	0.99	0.35, 2.83	0.99
5.	SOFA	0.95	0.85, 1.06	0.34

Nagelkerke R Square = 0.209, Hosmer-Lemeshow test value = 0.218 (good fit)

The addition of clinically relevant factors to the above models (Tables 15 & 16) paved way to models 3 & 4 (Tables 21 & 22). Male gender and the effects modifiers commonly

encountered in our study, namely aspirin and vitamin K, were the additional factors which were analyzed. Addition of these factors also appeared to increase the predictive ability of the model by nearly 10%. It was of interest that, in these models, in addition to central venous catheters; day 3 PT/INR and vitamin K administration emerged as statistically significant factors, independently associated with the development of DVT. The latter was protective against DVT and this was thought to be related to the underlying anticoagulant state in patients necessitating administration of vitamin K. Age more than forty years also emerged as a risk factor tending towards statistical significance (p=0.07). Both the models were found to be of adequate fit.

Table 21 - Multivariate Analysis - Risk factors for Development of DVT in MICU – Model 3

S.No.	Risk Factors	Relative Risk	95% CI	P Value
1.	*Central Venous Catheters*	13.72	1.59, 118.48	0.02
2.	*Day 3 INR*	4.23	1.15, 15.61	0.03
3.	Age > 40 yrs	2.57	0.93, 7.13	0.07
4.	Vasopressors	1.19	0.39, 3.59	0.74
5.	SOFA	0.95	0.85, 1.06	0.39
6.	Male Sex	1.30	0.55, 3.10	0.54
7.	*Vitamin K*	0.17	0.03, 0.92	0.04
8.	Aspirin	0.29	0.06, 1.47	0.14

Nagelkerke R Square = 0.278, Hosmer-Lemeshow test value = 0.415 (good fit)

Table 22 - Multivariate Analysis - Risk factors for Development of DVT in MICU – Model 4

S.No.	Risk Factors	Relative Risk	95% CI	P Value
1.	*Central Venous Catheters*	13.91	1.61, 120.05	0.02
2.	*Day 3 PT*	1.15	1.02, 1.29	0.03
3.	Age > 40 yrs	2.54	0.91, 7.08	0.07
4.	Vasopressors	1.17	0.39, 3.51	0.78
5.	SOFA	0.95	0.85, 1.07	0.40
6.	Male Sex	1.29	0.55, 3.09	0.55
7.	*Vitamin K*	0.16	0.03, 0.88	0.03
8.	Aspirin	0.30	0.06, 1.49	0.14

Nagelkerke R Square = 0.279, Hosmer-Lemeshow test value = 0.32 (good fit)

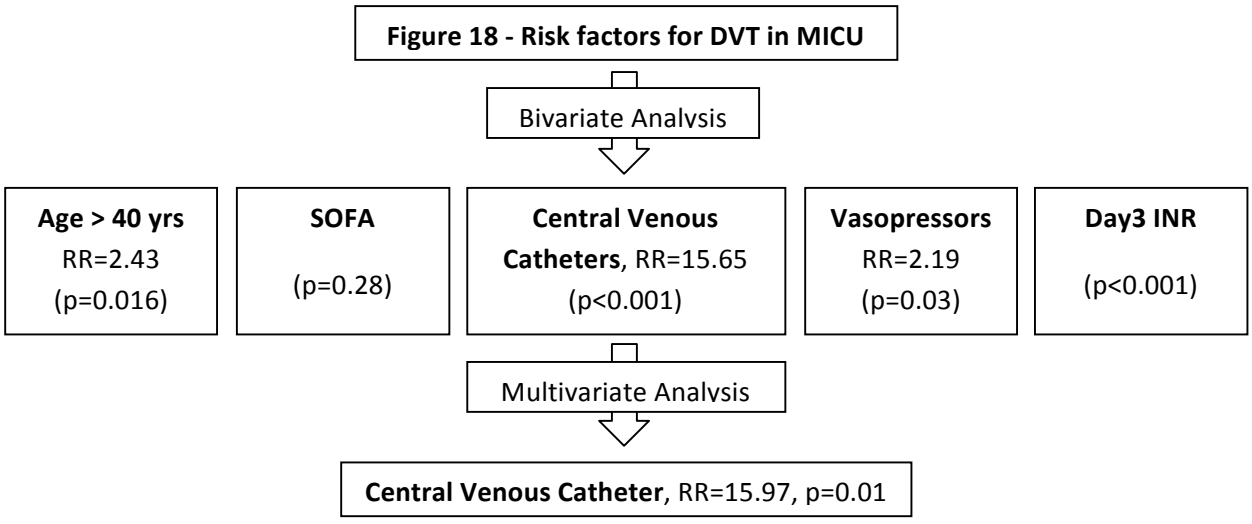
The fifth model (Table 23) was drawn by the inclusion of the relatively significant exposure variables to the fourth model. As none of the exposure variables were statistically

significant as risk factors on the bivariate analysis, two of those with the least p values were included to study their influence on the development of DVT. Amongst the exposure variables, alcohol, smoking and vitamin K were the ones commonly encountered in the entire study population. The variables which were relatively significant on the bivariate analysis were chronic kidney disease (p=0.57) and alcohol consumption (p=0.52). The observations however did not differ from the previous model although, this seemed to have the best predictive value.

Table 23 - Multivariate Analysis - Risk factors for Development of DVT in MICU – Model 4

S.No.	Risk Factors	Relative Risk	95% CI	P Value
1.	*Central Venous Catheters*	14.0	1.61, 122.12	0.02
2.	*Day 3 PT*	1.14	1.02, 1.29	0.02
3.	Age > 40 yrs	2.81	0.99, 7.97	0.05
4.	Vasopressors	1.11	0.37, 3.38	0.85
5.	SOFA	0.95	0.85, 1.07	0.39
6.	Male Sex	1.08	0.41, 2.88	0.88
7.	*Vitamin K*	0.15	0.03, 0.82	0.03
8.	Aspirin	0.29	0.06, 1.52	0.31
9.	Chronic Kidney Disease	0.32	0.04, 2.88	0.31
10.	Alcohol	0.57	0.15, 2.13	0.40

Nagelkerke R Square = 0.293, Hosmer-Lemeshow test value = 0.89 (good fit)



RISK FACTORS FOR THE DEVELOPMENT OF NON CATHETER RELATED DVT IN THE MEDICAL ICU

The presence of central venous catheters had been seen in 154 patients (70.2 % of the study population). 24.4% (n=34/139) of patients on central venous catheters had developed DVT in the MICU. Of those who had developed a DVT in the MICU, 97.1% (n=34/35) had a central venous catheter. In the non DVT group, this was seen in 62.5% patients (n=105/168).

In the bivariate analysis of risk factors for development of DVT in the MICU, the strongest risk factor had been the presence of a central venous catheter (15.65, (2.11, 111.8)), which had again emerged as the only factor independently associated with DVT development on logistic regression. Further, the catheter related DVTs had contributed to nearly two-thirds of the incident DVTs (n=23/35). Therefore, this was thought to have had a large influence on the distribution of risk factors, although the secondary outcomes were apparently similar in patients with catheter related and non-catheter related DVTs.

Hence, risk factor analysis of the non catheter related DVTs was done in order to identify the other risk factors involved in their development. The large number of catheter related DVTs and hence, the strong association with the presence of central venous catheters, was thought to have overshadowed the other factors. The bivariate analysis (Table 24) identified the following risk factors for the development of a catheter related DVT in the MICU:

1) Central venous catheter, RR = 6.06 (0.8, 45.9), p=0.08
2) Age > 40 years, RR = 3.9 (0.88, 17.2), p=0.095
3) Day 3 PT (p=0.08) & INR (p=0.09)
4) Day 1 platelet counts (p=0.006)

The ones which were statistically significant ($p<0.05$) included the presence of a jugular catheter (3.62, (1.14, 11.57)), mean duration of central venous catheter and the platelet counts on day1. As the number of variates that had emerged statistically significant (in the bivariate analysis) was very small, all risk factors with a p value of less than 10% (above listed) were considered for the multivariate analysis (Table 24). It was interesting to note that among the central venous catheters, the femoral catheters seemed to confer the strongest risk to the development of DVT in MICU, while the jugular catheters appeared to be strongly implicated in the development of non catheter related DVT.

Table 24–Bivariate Analysis-Risk factors for development of non catheter related DVT in MICU

Risk factors (n=203)	Incident Non catheter related DVT (n=12) n (%)	Non DVT (n=168) n (%)	RR	95% CI	P value
Mean Age (yrs)	53 ± 13.07	43.99 ± 17.84			
Age <40 yrs	2 (2.5)	77 (97.5)			
Age >40 yrs	10 (10)	91 (90)	**3.91**	0.88, 17.24	0.095
Male gender	6 (6)	95 (94)	0.78	0.26, 2.33	0.88
Female gender	6 (8)	73 (92)			
Past history					
Surgery (within 4 wks)	1 (8)	11 (92)	1.27	0.18, 9.04	0.719
Trauma (within 4 wks)	---	3 (100)			
Hospitalization (>3days)	4 (12)	30 (88)	2.14	0.69, 6.72	0.346
Central catheters	2 (50)	2 (50)			
NSAID use	---	2 (100)			
Rheumatic / autoimmune disease	1 (10)	10 (90)	1.40	0.20, 9.86	0.77
Present history					
Congestive cardiac failure	---	8 (100)			
Chronic liver failure	---	6 (100)			
Chronic kidney disease	1 (8)	12 (92)	1.16	0.16, 8.35	0.67
Malignancy	---	1 (100)			
Post partum	---	6 (100)			
Immobilization (stroke/paresis)	1 (17)	5 (83)	2.63	0.40, 17.25	0.867
Pacemaker Insertion	---	2 (100)			
Smoking	3 (10)	26 (90)	1.73	0.50, 6.02	0.645
Alcohol	3 (7)	40 (93)	1.06	0.30, 3.74	0.797
Aspirin	1 (5)	21 (95)	0.65	0.08, 4.81	0.975
Clopidogrel	1 (6)	15 (94)	0.93	0.12, 6.76	0.649
Vitamin K supplements	---	28 (100)			
Other comorbidities	6 (8)	73 (92)	1.27	0.43, 3.81	0.888
SOFA score at admission to ICU	7.75 ± 1.14	6.90 ± 4.30		-3.37, 1.67	0.506

Symptoms of DVT	1 (20)	4 (80)	3.18	0.5, 20.1	0.761
Treatment in ICU					
Central Venous catheters	11 (9)	105 (91)	**6.06**	0.80, 45.94	0.08
Internal Jugular	8 (13)	56 (87)	3.62	1.14, 11.57	0.043
Subclavian	1 (20)	4 (80)	3.18	0.5, 20.11	0.761
Femoral	2 (4)	45 (96)	0.56	0.1, 2.48	0.666
Mean duration (days)	9 ± 3.9	6.96 ± 2.97		0.11, 3.96	0.03
Peripherally inserted central catheters	1 (33)	2 (67)	5.36	0.98, 29.34	0.483
Mean duration (days)	10	5.50 ± 0.70		-6.5, 15.5	0.121
Dialysis ports	1 (10)	9 (90)	1.54	0.22, 10.81	0.827
Jugular	---	2 (100)			
Femoral	1 (13)	7 (87)	1.95	0.28, 13.33	0.961
Mean duration (days)	15	8.44 ± 4.87		-5.30, 18.4	0.238
Mechanical ventilation	9 (7)	129 (93)	0.91	0.25, 3.21	0.83
Mean duration (days)	9.56 ± 6.31	7.32 ± 5.16		-1.33, 5.81	0.217
Sedatives	7 (6)	107 (94)	0.81	0.27, 2.45	0.95
Mean duration (days)	5 ± 2.58	3.64 ± 2.74		-0.75, 3.48	0.203
Muscle relaxants					
Vasopressors	8 (9)	83 (91)	1.95	0.61, 6.27	0.391
Dopamine	---	2 (100)			
Adrenaline	3 (14)	19 (86)	2.39	0.7, 8.16	0.345
Noradrenaline	2 (7)	29 (93)	0.96	0.22, 4.17	0.731
Dobutamine	---	2 (100)			
Multiple	3 (9)	31 (91)	1.43	0.40, 5.00	0.858
Mean duration (days)	4.38 ± 2.13	4.04 ± 2.92		-1.78, 2.45	0.751
Transfusions	2 (8.0)	23 (92.0)	1.24	0.28, 5.33	0.885
Packed cells	1 (13)	7 (87)	1.95	0.29, 13.33	0.961
Platelets	1 (25)	3 (75)	4.00	0.66, 23.98	0.636
FFP	---	3			
Multiple	---	10			
Laboratory investigations					
Mean PT					
D1	13.04 ± 2.06	14.03 ± 6.01		-4.77, 2.80	0.607
D3	15.37 ± 2.97	13.3 ± 3.60		-0.24, 4.34	**0.080**

D7	13.48 ± 2.71	12.59 ± 4.10		-1.6, 3.39	0.481
Mean INR					
D1	1.184 ± 0.18	1.27 ± 0.53		-0.41, 0.24	0.604
D3	1.39 ± 0.26	1.21 ± 0.32		-0.02, 0.38	**0.090**
D7	1.22 ± 0.23	1.14 ± 0.35		-0.13, 0.29	0.477
Mean APTT					
D1	31.93 ± 5.76	32.9 ± 12.77		-9.03, 7.08	0.812
D3	38.23 ± 7.69	32.84 ± 12.68		-2.64, 13.4	0.187
D7	36.52 ± 11.96	32.03 ± 10.56		-2.15, 11.1	0.184
Mean platelet counts					
D1 (Mean , SD)	3.37L ± 2.22L	2.14L ± 1.35L		0.35, 2.1	**0.006**
(Median, IQR)	3L (1.6, 5.5)	2.08 L(1.1,3.1)			
D3 (Mean , SD)	2.63L ± 1.97L	2.25L ± 2.53L		-1.15, 1.91	0.625
(Median, IQR)	2.4L (1.2, 4.6)	1.9L (0.8, 2.9)			
D7 (Mean , SD)	2.17L ± 1.49L	1.91 ± 1.23L		-0.52, 1.04	0.510
(Median, IQR)	1.68L (1.2, 2.8)	1.8L (0.93, 2.6)			
D1 platelets <100000	3 (4)	72 (96)	1.96	0.54, 7.14	0.464
D1 platelets >100000	8 (8)	94 (92)			
D1 platelets <180000	2 (5)	40 (95)	1.4	0.31, 6.22	0.935
D1 platelets >180000	9 (7)	126 (93)			
Thromboprophylaxis	12 (100)	168 (100)			
Pharmacological	9 (9)	95 (91)	2.19	0.61, 7.82	0.343
Heparin	9 (9)	95 (91)	2.19	0.61, 7.82	0.343
Enoxaparin	---	5			
Adequate dosage	9 (100)	95 (100)			
Mechanical	3 (4)	68 (96)	0.51	0.14, 1.82	0.45
Both	---	5			

No comparisons were made as one of the arms either had complete absence of the risk factor, or the occurrence was equal in both the arms.

IQR=interquartile range, SD=standard deviation, PIC=peripherally inserted central catheters.

PT and APTT have been given in seconds and platelets in lakhs.

INDEPENDENT RISK FACTORS FOR THE DEVELOPMENT OF NON CATHETER RELATED DVT IN MEDICAL ICU

Logistic regression was done for the risk factors which had atleast 10% significance ($p<0.1$) in the bivariate analysis. This included the presence of central venous catheter, age more than forty years, day 3 PT and day 1 platelet count. In addition, SOFA score was included to adjust for severity of co morbidities.

In the first model (Table 25), although central venous catheters and age emerged as risk factors, they were not statistically significant. This model was of adequate fit and predicted 22% of the variability. The only variable which was statistically significant was the platelet count on day 1. The relative risk for the same was one, implying no risk. Hence, a second model (Table 26) was done excluding them, the outcomes of which were not statistically significant.

As platelet counts at day 1 had emerged significant in the first model, despite there being no risk per se, categorization of the same was done. A third model was designed, based on the second model with the inclusion of platelets counts of more than one lakh at day 1, as this was thought to be more clinically relevant (Table 27). Furthermore, as the median value of the day 1 platelet count was nearly 1.8 lakhs, it was again categorized based on this value, creating the fourth model (table 28). Similar results were observed in these models too, wherein, central venous catheters and age had turned up as risk factors, but were not statistically significant.

As none of the factors were independently associated with the development of non catheter related DVT, the small event rate was thought to be responsible. A retrospective power analysis was done (from model 3), which showed that the power estimated was 52%.

Therefore, it was concluded that a larger event rate would have been required to adequately power the study.

Table 25 - Multivariate Analysis-Risk factors for Non catheter related DVT in MICU–Model 1

S.No.	Risk Factors	Relative Risk	95% CI	P Value
1.	Central Venous Catheters	3.27	0.36, 30.0	0.29
2.	Age > 40 yrs	4.31	0.49, 37.49	0.19
3.	Day 1 platelet count	1.00	1.00, 1.00	0.02
4.	Day 3 PT	1.12	0.97, 1.29	0.13
5.	SOFA	1.05	0.85, 1.29	0.66

Nagelkerke R Square = 0.228, Hosmer-Lemeshow test value = 0.264 (good fit)

Table 26 - Multivariate Analysis-Risk factors for Non catheter related DVT in MICU–Model 2

S.No.	Risk Factors	Relative Risk	95% CI	P Value
1.	Central Venous Catheters	4.04	0.46, 35.65	0.21
2.	Age > 40 yrs	5.99	0.71, 50.54	0.10
3.	Day 3 PT	1.10	0.96, 1.26	0.16
4.	SOFA	0.94	0.79, 1.11	0.45

Nagelkerke R Square = 0.148, Hosmer-Lemeshow test value = 0.286 (good fit)

Table 27 - Multivariate Analysis-Risk factors for Non catheter related DVT in MICU–Model 3

S.No.	Risk Factors	Relative Risk	95% CI	P Value
1.	Central Venous Catheters	4.16	0.47, 36.92	0.20
2.	Age > 40 yrs	5.68	0.66, 48.49	0.11
3.	Day 1 platelet count > 1 lakh	1.78	0.29, 11.04	0.53
4.	Day 3 PT	1.1	0.96, 1.26	0.17
5.	SOFA	0.96	0.79, 1.16	0.69

Nagelkerke R Square = 0.153, Hosmer-Lemeshow test value = 0.28 (good fit)

Table 28 - Multivariate Analysis-Risk factors for Non catheter related DVT in MICU–Model 4

S.No.	Risk Factors	Relative Risk	95% CI	P Value
1.	Central Venous Catheters	4.15	0.47, 36.82	0.20
2.	Age > 40 yrs	5.82	0.68, 49.45	0.11
3.	Day 1 platelet count > 1.8 lakh	3.06	0.58, 16.24	0.19
4.	Day 3 PT	1.12	0.97, 1.28	0.12
5.	SOFA	0.99	0.82, 1.19	0.93

Nagelkerke R Square = 0.176, Hosmer-Lemeshow test value = 0.55 (good fit)

RISK FACTORS FOR IN-HOSPITAL MORTALITY IN PATIENTS GETTING ADMITTED TO THE MEDICAL ICU

The risk factors for in-hospital mortality were studied amongst these patients, in order to determine the clinical relevance of these deep venous thrombi. It was intriguing to determine if these venous thrombi, which occurred in the patients getting admitted to the medical intensive care, despite being on thromboprophylaxis, posed a clinically significant threat to the outcomes of these patients. Therefore, risk factor analysis was done in all patients included in the study, excluding the discharges against medical advice. The risk factors and the presence of DVT were compared between the mortality group (in hospital deaths) and the survivor group (discharged alive from the hospital). Bivariate analysis (Table 29) revealed the following factors to be the significant predictors of in-hospital mortality for patients getting admitted to the medical intensive care facility:

1) Mechanical Ventilation, 3.83 (1.46, 10.07), p=0.02
2) Use of Vasopressors, 3.26 (1.78, 5.95), p<0.001
3) Central Venous Catheters, 2.8 (1.34, 5.85), p=0.003
4) Use of Sedatives, 2.19 (1.23, 6.32), p=0.006
5) Transfusions, 1.91 (1.16, 3.12), p=0.03
6) Mechanic thromboprophylaxis, 1.86 (1.17, 2.95), p=0.01
7) Age > 40yrs, 1.63 (1.0, 2.67), p=0.06
8) Pharmacological thromboprophylaxis, 0.54 (0.33, 0.86), p=0.01
9) SOFA score, (1.46, 4.19), p=0.01
10) Day3 PT/INR (0.03, 3.23), p=0.04
11) Day3 APTT (1.85, 12.27), p=0.009

It was seen that most of the risk factors for in-hospital mortality were surrogate markers of severity of illness (necessitating intensive care management), like, the need for mechanical ventilation, inotropic supports, central venous catheters, transfusions and SOFA score. It was interesting to note that specifically, those on femoral venous catheters (2.3), receiving multiple vasopressors (2.8) and multiple transfusions (2.37), seemed to be a higher risk. It was also interesting to find that while pharmacological thromboprophylaxis was a significant protective factor against in-hospital mortality; mechanical thromboprophylaxis was associated with adverse outcomes. This could be attributed to the factors pre-existent in the patient, which might preclude the use of pharmacological prophylaxis, like coagulopathy, which could indicate an underlying multi-organ dysfunction or a severe sepsis syndrome. The day 3 PT and APTT also seemed to play a significant role.

Table 29 – Bivariate Analysis – Risk factors for In-Hospital mortality in patients getting admitted to the MICU

Risk factors (n=200) [19 DAMA; 219-19=200]	Mortality (n=54) n (%)	Survivors (n=146) n (%)	Relative Risk	95% CI	P value
Mean Age (yrs)	48.28±16.36	42.48±17.07		0.49, 11.10	0.032
Age >40 yrs	36 (33.3)	74 (66.7)	**1.63**	1.0, 2.67	0.06
Age <40 yrs	18 (20)	72 (80)			
Male gender	34 (31)	77 (69)	1.36	0.84, 2.11	0.257
Female gender	20 (23)	69 (77)			
Past history					
Surgery (within 4 wks)	4 (33)	8 (67)	1.25	0.54, 2.89	0.86
Trauma (within 4 wks)	1 (25)	3 (75)	0.92	0.16, 5.12	0.63
Hospitalization (>3days)	13 (36)	23 (64)	1.44	0.86, 2.40	0.24
Central catheters	1 (50)	1 (50)	-		
NSAID use	1 (50)	1 (50)	-		
Rheumatic / autoimmune	4 (27)	11 (73)	0.98	0.41, 2.35	0.78
Present history					
Congestive cardiac failure	2 (29)	5 (71)	1.06	0.32, 3.5	0.74
Chronic liver failure	2 (33)	4 (67)	1.24	0.39, 3.94	0.91
Chronic kidney disease	3 (27)	8 (73)	1.01	0.37, 2.72	0.74
Malignancy	1 (100)	-			
Post partum	3 (43)	4 (57)	1.62	0.66, 3.93	0.59
Immobilization	3 (60)	2 (40)	2.29	1.07, 4.87	0.24
Pacemaker Insertion	-	4 (100)	-		
Smoking	10 (32)	21 (68)	1.23	0.7, 2.19	0.61
Alcohol	9 (21)	34 (79)	0.73	0.38, 1.37	0.41
Aspirin	7 (30)	16 (70)	1.14	0.58, 2.22	0.88
Clopidogrel	6 (33)	12 (67)	1.26	0.62, 2.53	0.72
Vitamin K supplements	13 (38)	21 (62)	1.54	0.93, 2.56	0.15
Other comorbidities	32 (34)	62 (66)	1.64	1.02, 2.61	0.05
SOFA score at admission to ICU	**9.25±4.44**	**6.43±3.93**		**1.46, 4.19**	**0.01**
Symptoms of DVT	2 (33)	4 (67)	1.24	0.39, 3.94	0.91

Treatment in ICU					
Central Venous catheters	47 (33)	94 (67)	**2.80**	1.34, 5.85	0.003
Internal Jugular	18 (26)	50 (74)	0.97	0.59, 1.57	0.96
Right	17 (26)	48 (74)	0.95	0.58, 1.56	0.98
Left	1 (33)	2 (67)	1.23	0.24, 6.24	0.68
Subclavian	-	6			
Right	-	5 (100)			
Left	-	1 (100)			
Femoral	29 (43)	38 (57)	2.30	1.47, 3.6	<0.001
Right	27 (45)	33 (55)	2.33	1.5, 3.62	<0.001
Left	2 (29)	5 (71)	1.06	0.32, 3.5	0.73
Mean duration (days)	7.11±3.57	7.29±2.76		-1.26, 0.89	0.75
PIC catheters	-	1 (100)			
Right					
Left	-	1 (100)			
Mean duration (days)		5			
Dialysis ports	3 (19)	13 (81)	0.67	0.23, 1.92	0.63
Jugular	1 (25)	3 (75)	0.92	0.16, 5.12	0.63
Right	-	1 (100)			
Left	1 (33)	2 (67)	1.23	0.24, 6.24	0.68
Femoral	2 (17)	10 (83)	0.60	0.16, 2.18	0.61
Right	-	6 (100)	-		
Left	2 (33)	4 (67)	1.24	0.39, 3.94	0.91
Mean duration (days)	5.0±2.6	10.0±4.89		-11.38, 1.38	0.115
Mechanical ventilation	50 (33)	103 (67)	**3.83**	1.46, 10.07	0.002
Mean duration (days)	8.48±5.04	6.78±4.94		-0.03, 3.39	0.050
Sedatives	42 (34)	81 (66)	**2.19**	1.23, 6.32	0.006
Mean duration (days)	3.93±2.24	3.46±2.48		-0.43, 1.37	0.30
Vasopressors	43 (39)	66 (61)	**3.26**	1.78, 5.95	<0.001
Dopamine	1 (25)	3 (75)	0.92	0.16, 5.1	0.63
Adrenaline	7 (32)	15 (68)	1.20	0.62, 2.32	0.77
Noradrenaline	10 (29)	25 (71)	1.07	0.51, 1.91	0.98
Dobutamine	-	1 (100)	-		
Multiple	25 (53)	22 (47)	2.8	1.83, 4.28	<0.001
Mean duration (days)	4.44±2.78	3.64±2.08		-0.12, 1.73	0.087
Transfusions	12 (46)	14 (54)	**1.91**	1.16, 3.12	0.03
Packed cells	2 (25)	6 (75)	0.92	0.27, 3.13	0.78
Whole blood	1 (100)	-	-		

Platelets	2 (50)	2 (50)	-		
FFP	1 (33)	2 (67)	1.23	0.24, 6.24	0.68
Multiple	6 (60)	4 (40)	2.37	1.35, 4.16	0.04
Laboratory investigations					
Mean PT					
D1	16.10±13.07	14.32±7.38		-1.31, 4.87	0.25
D3	14.94±5.0	13.3±4.99		0.03, 3.23	**0.045**
D7	13.63±7.12	12.2±1.73		-0.98, 3.80	0.24
Mean INR					
D1	1.47±1.28	1.21±0.62		-0.10, 0.46	0.21
D3	1.35±0.45	1.20±0.45		0.003, 0.29	**0.04**
D7	1.23±0.60	1.11±0.15		-0.09, 0.32	0.26
Mean APTT					
D1	36.11±16.29	33.02±12.89		-1.58, 7.76	0.19
D3	38.12±18.24	31.06±8.31		1.85, 12.27	**0.009**
D7	32.23±8.12	32.63±12.44		-4.8, 4.01	0.857
Mean platelet counts					
D1	1.91 ± 1.64	2.17 ± 1.36		-0.71,0.20	0.27
D3	1.88 ± 2.59	2.24 ± 2.33		-1.11, 0.40	0.35
D7	1.72 ± 1.44	1.93 ± 1.11		-0.66, 0.22	0.33
Thromboprophylaxis	54 (27)	146 (73)			
Pharmacological	22 (20)	90 (80)	**0.54**	0.33, 0.86	0.01
Heparin	19 (18)	87 (82)	0.48	0.29, 0.78	0.003
Enoxaparin	3 (50)	3 (50)	-		
Mechanical	31 (37)	53 (63)	**1.86**	1.17, 2.95	0.01
Both*	1 (25)	3 (75)	0.92	0.16, 5.12	0.63
Duration of ICU stay	8.44 ± 5.5	6.83 ± 5.35		-0.08, 3.30	0.063
Duration of Hospital stay	15.39 ± 15.15	14.65 ± 9.35		-2.78, 4.25	0.69
Mean time of DVT development from admission into MICU	3.14 ± 2.28	2.75 ± 0.67		-0.81, 1.6	0.515
Mean time of DVT development from admission into Hospital	7.71 ± 9.16	5.31 ± 5.31		-1.84, 6.79	0.255
Presence of DVT	14 (30)	32 (70)	1.17	0.70, 1.95	0.68
ICU Incident DVT (D3 + D7)	9 (29)	22 (71)	1.09	0.59, 1.99	0.95
D1 DVT	5 (33)	10 (67)	1.25	0.59, 2.67	0.78
Non Catheter related DVT	3 (25)	9 (75)	0.92	0.33, 2.52	0.86

No comparisons were made as one of the arms either had complete absence of the risk factor, or the occurrence was equal in both the arms.

IQR=interquartile range, SD=standard deviation, PIC=peripherally inserted central catheters.

PT and APTT have been given in seconds and platelets in lakhs.

The presence of DVT was also compared between the two groups to look for any influence exerted by the former on mortality. Nearly 30% of those who had developed a DVT in the medical ICU had unfavourable hospital outcomes. The presence of DVT per se appeared to confer risk (1.17), but this was not statistically significant. Amongst the DVTs, the day 1 DVTs appeared to confer higher risk (1.25), than the incident DVTs (1.09); however the differences were not statistically significant.

INDEPENDENT RISK FACTORS FOR IN-HOSPITAL MORTALITY IN THE MEDICAL INTENSIVE CARE UNIT

It was seen in the multivariate analysis that only mechanical ventilation and day 3 APTT turned out as independent predictors of in-hospital mortality in patients getting admitted to the medical intensive care. This model was of good fit and could predict 30% of the variability.

Table 30 - Multivariate Analysis - Risk factors for In-Hospital mortality in patients getting admitted to the MICU

S.No.	Risk Factors	Relative Risk	95% CI	P Value
1.	*Mechanical Ventilation*	6.31	1.22, 32.58	0.028
2.	Vasopressors	2.28	0.72, 7.2	0.16
3.	Transfusions	2.18	0.75, 6.38	0.15
4.	Sedatives	1.47	0.54, 4.02	0.45
5.	Central Venous Catheters	1.32	0.36, 4.84	0.68
6.	Age >40 yrs	1.13	0.51, 2.54	0.77
7.	SOFA score	1.07	0.97, 1.19	0.18
8.	*Day 3 APTT*	1.05	1.002, 1.092	0.04
9.	Day 3 INR	0.54	0.19, 1.46	0.22
10.	Pharmacological Thromboprophylaxis	0.58	0.04, 7.75	0.68
11.	Mechanical Thromboprophylaxis	0.65	0.05, 9.1	0.75

Nagelkerke R Square = 0.301, Hosmer-Lemeshow test value = 0.132 (good fit)

PROBABILITY OF DVT FREE SURVIVAL IN THE MEDICAL ICU

It was seen that the overall probability of DVT free survival in the medical ICU came down as the duration of the ICU stay increased, with the steepest drop being observed at around day 3 of ICU stay (Figure 19). This was consistent with the mean duration of ICU stay at DVT development, which was determined to be 3.8 ± 1.6 days. Similar DVT free survival curves were drawn for age, gender and other ICU related exposure factors (Figures 20-27). Statistically significant differences were observed with age ($p=0.02$), central venous catheters ($p<0.001$), dialysis ports ($p=0.008$) and vasopressors ($p=0.021$). It was seen that the probability of DVT free survival in the medical ICU was lesser for those above the age of forty years (Figure 20) and those on central venous catheters (Figure 22), dialysis ports (Figure 23) or vasopressors (Figure 24).

Figure 19 - Probability of DVT free survival in the MICU

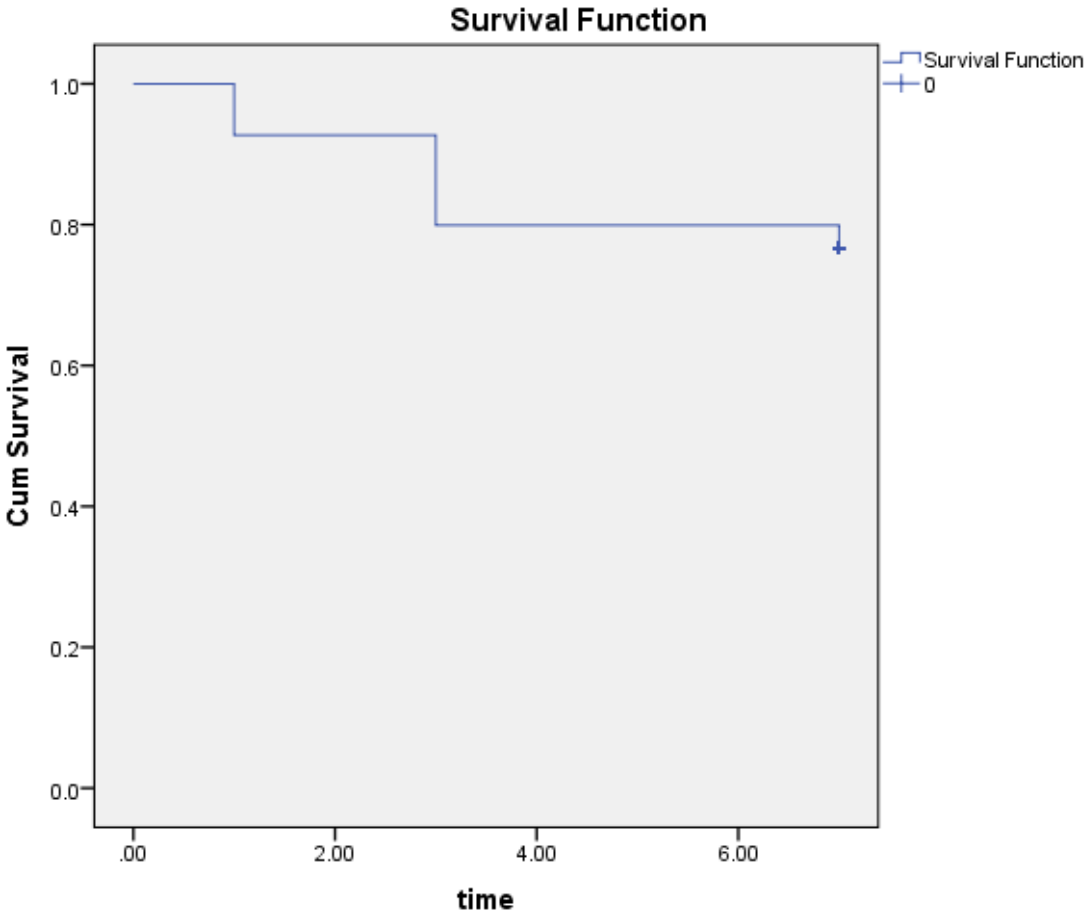


Figure 20 – Effect of Age on the Probability of DVT free survival in the MICU (p=0.02)

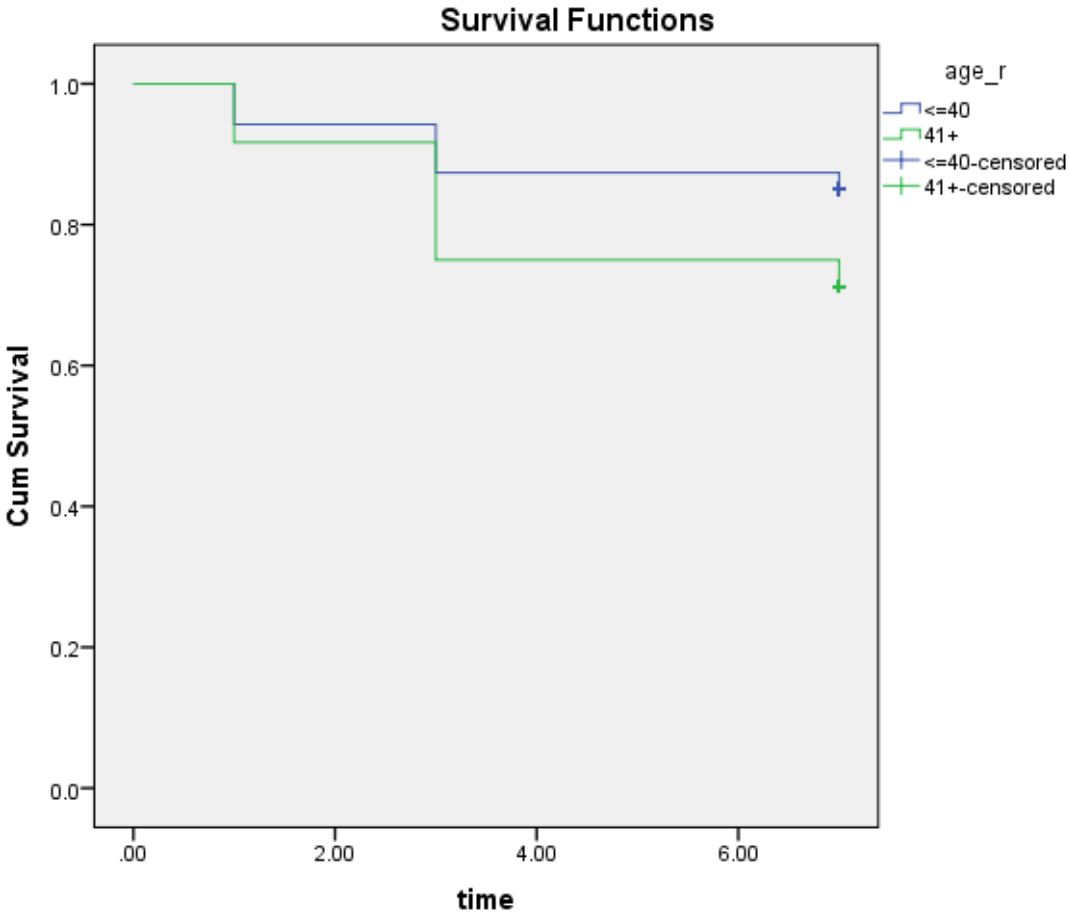


Figure 21 – Effect of Gender on the Probability of DVT free survival in the MICU (p=0.49)

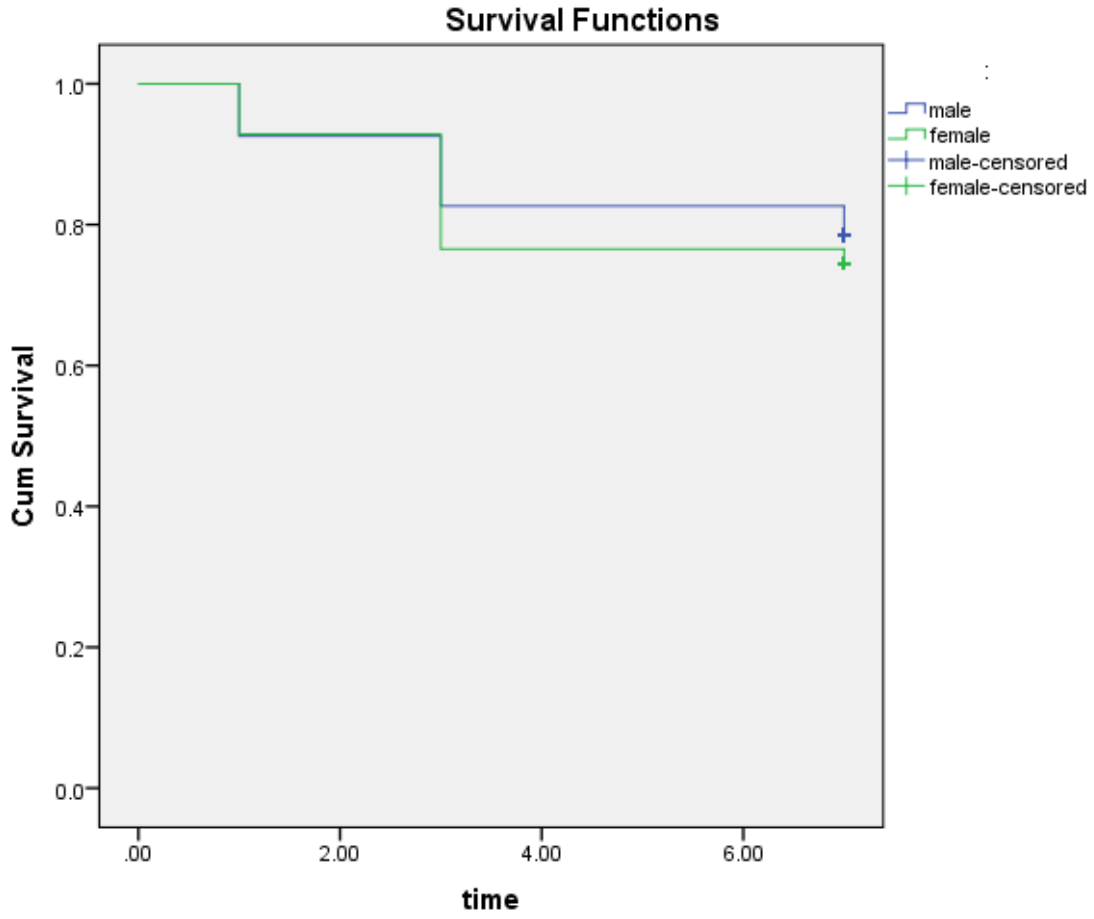


Figure 22 – Effect of Central Venous Catheters on the Probability of DVT free survival in the MICU (p<0.001)

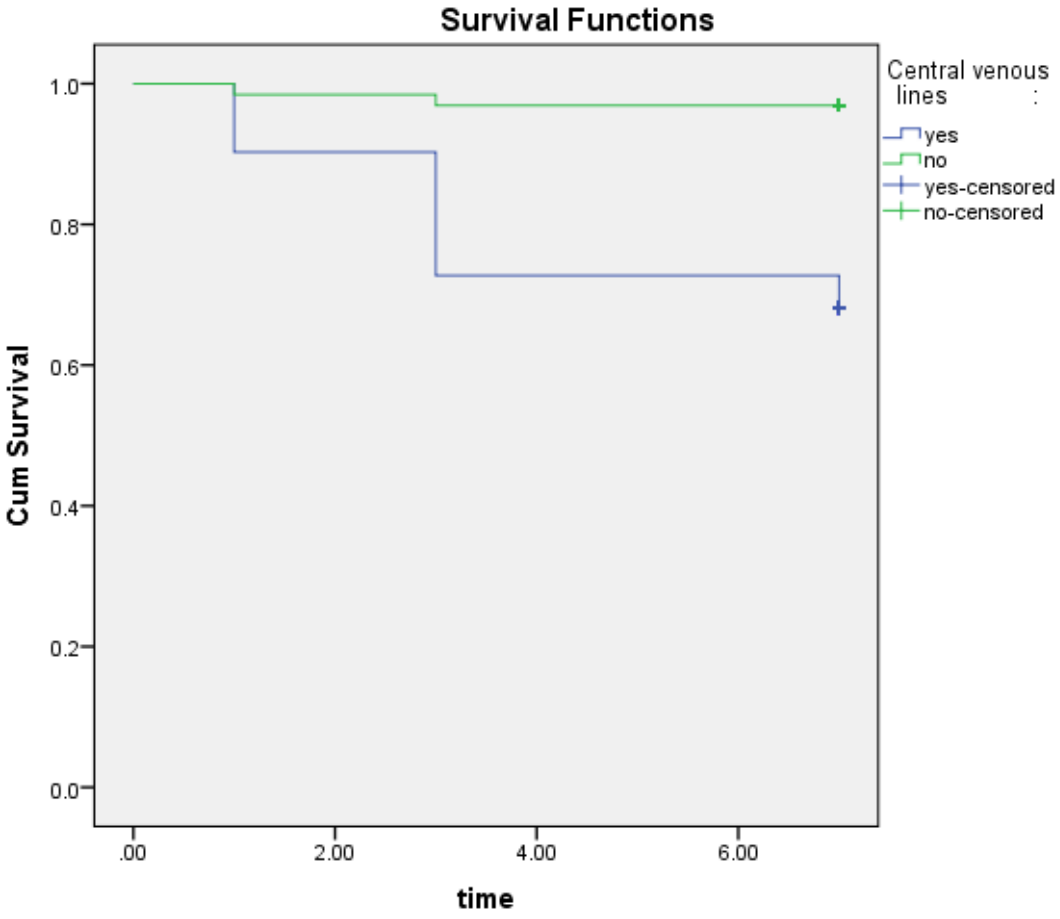


Figure 23 – Effect of Dialysis ports on the Probability of DVT free survival in the MICU (p=0.008)

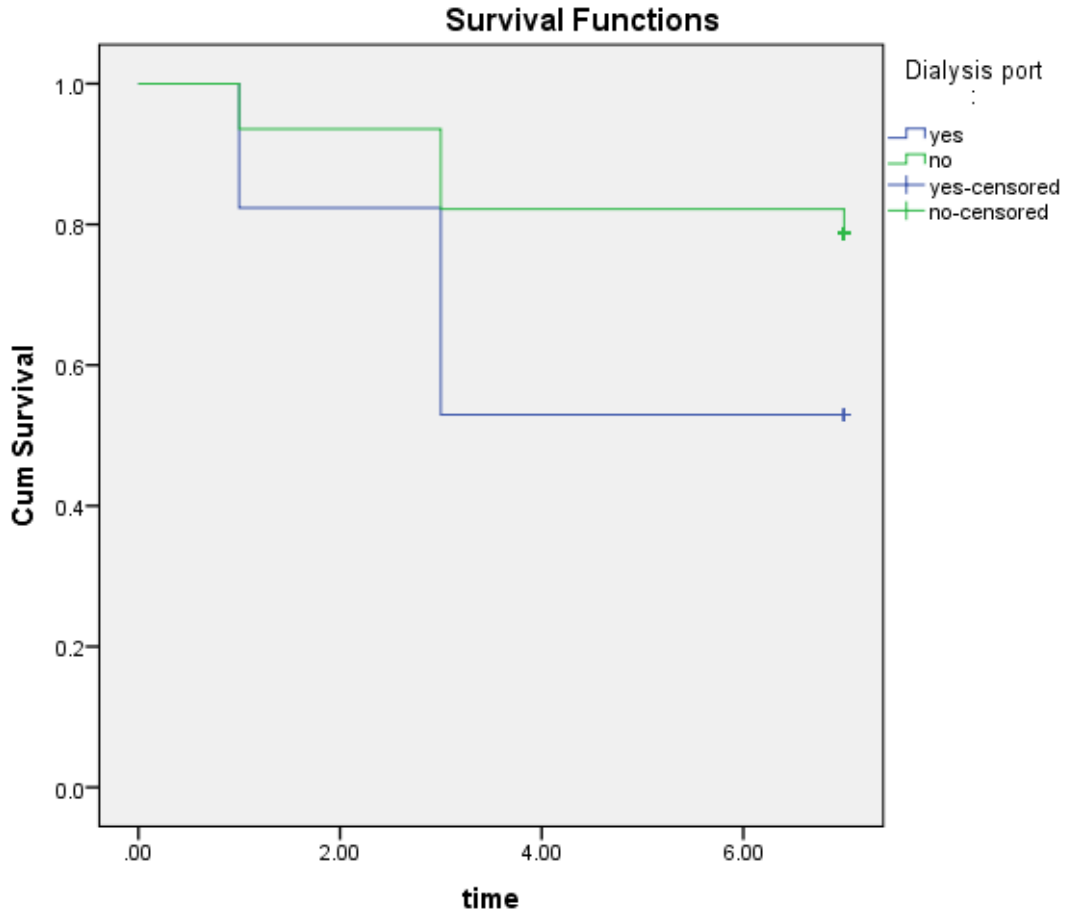


Figure 24 – Effect of Vasopressors on the Probability of DVT free survival in the MICU (p=0.021)

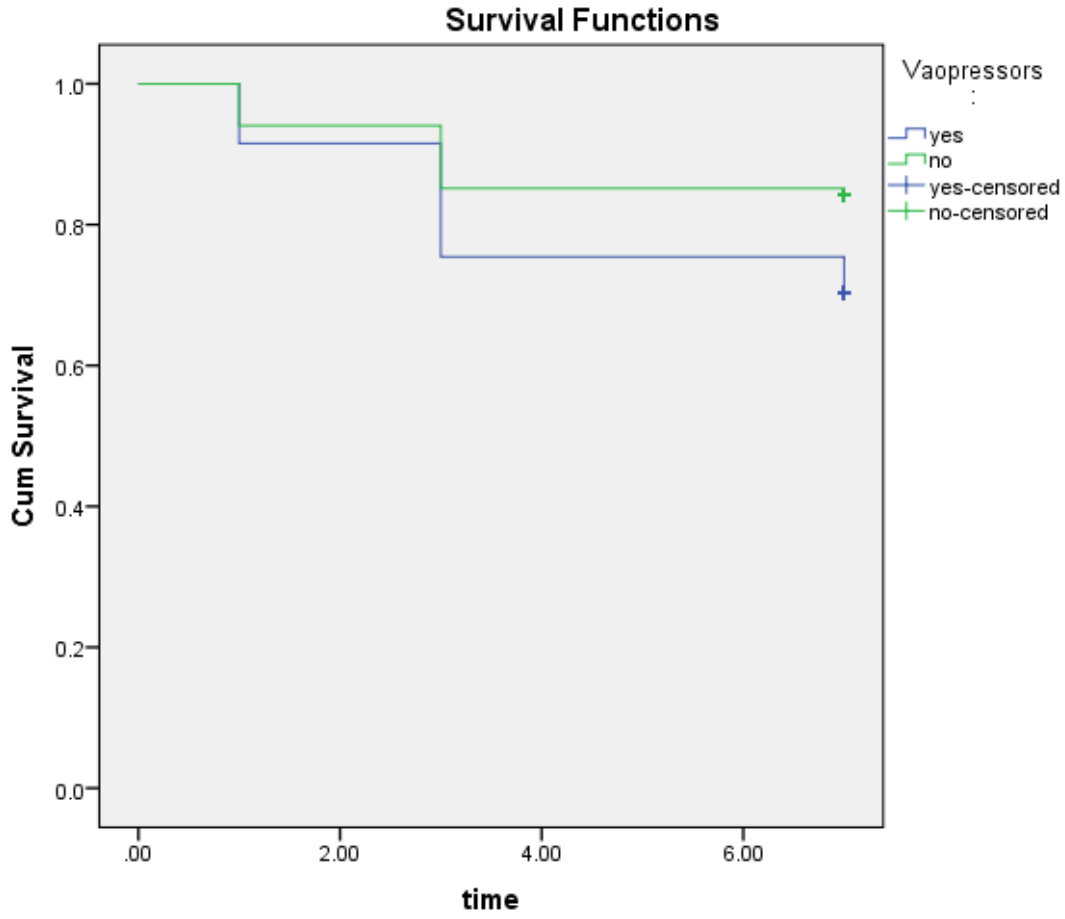


Figure 25 – Effect of Mechanical Ventilation on the Probability of DVT free survival in the MICU (p=0.345)

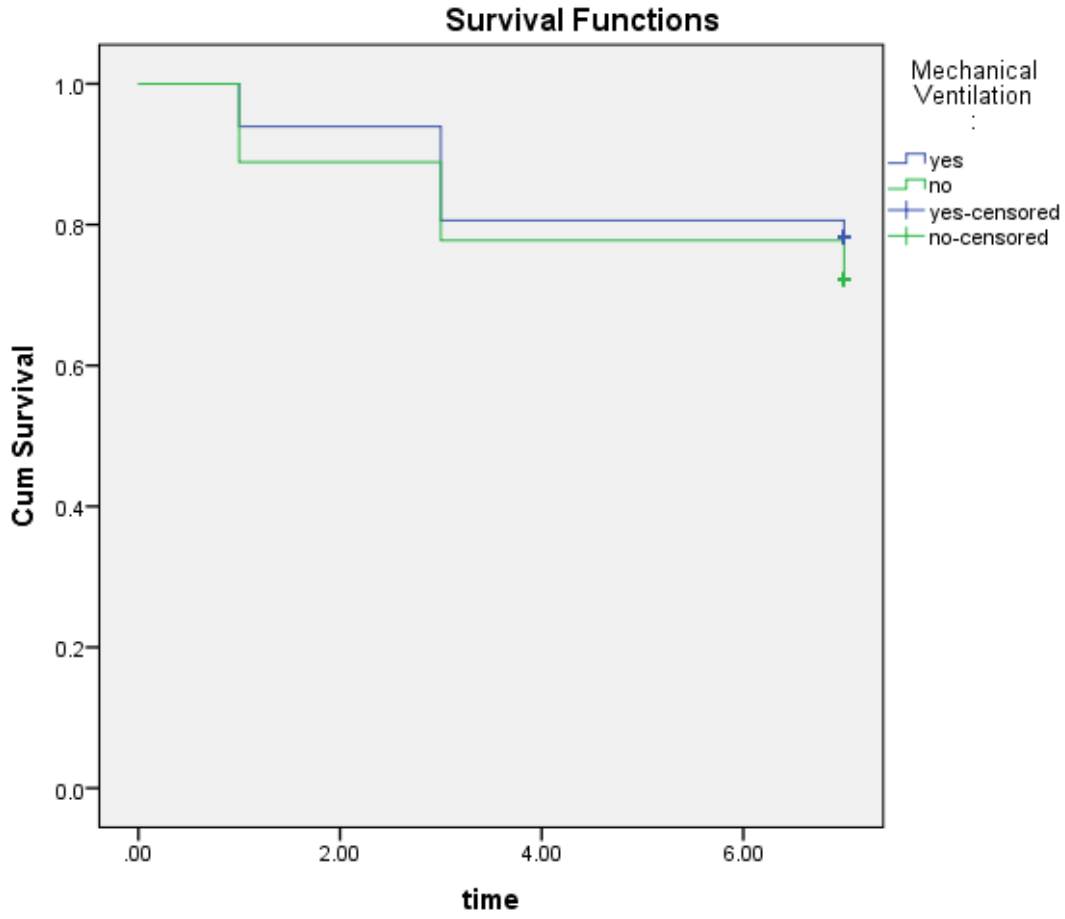


Figure 26 – Effect of Transfusions on the Probability of DVT free survival in the MICU (p=0.639)

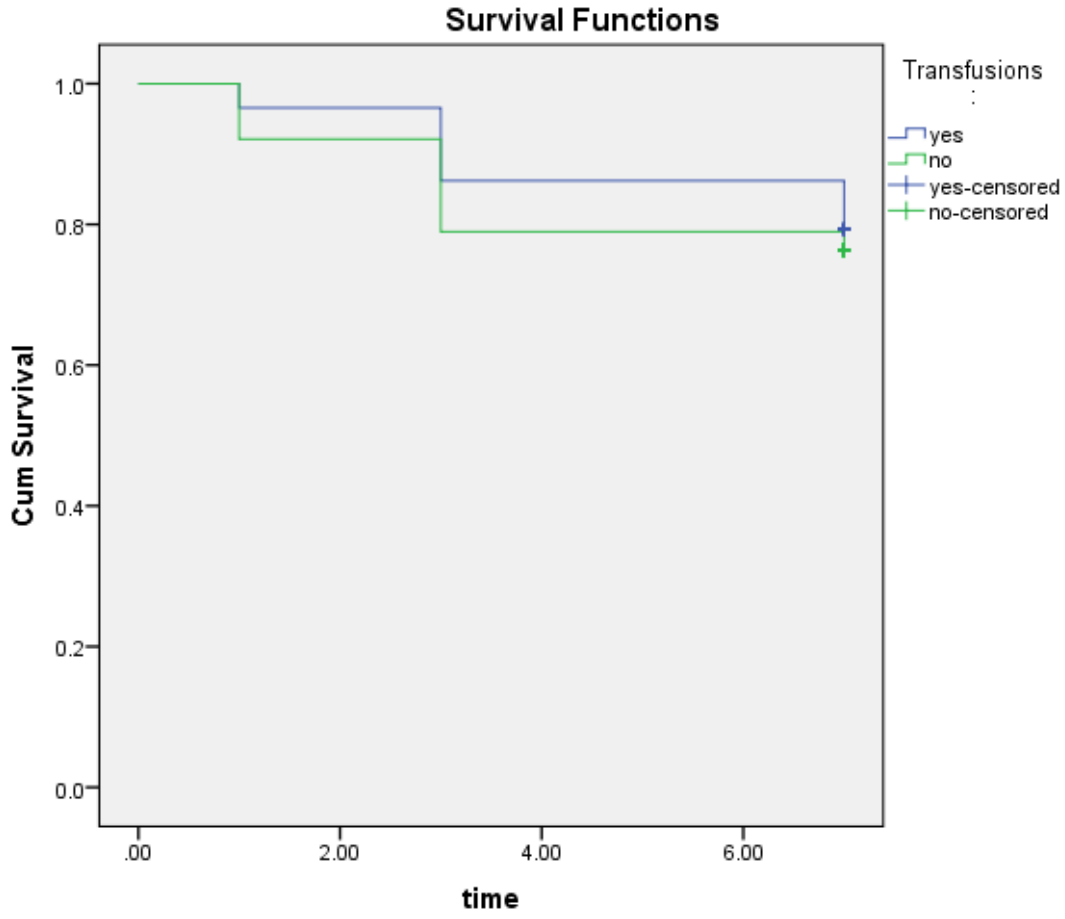
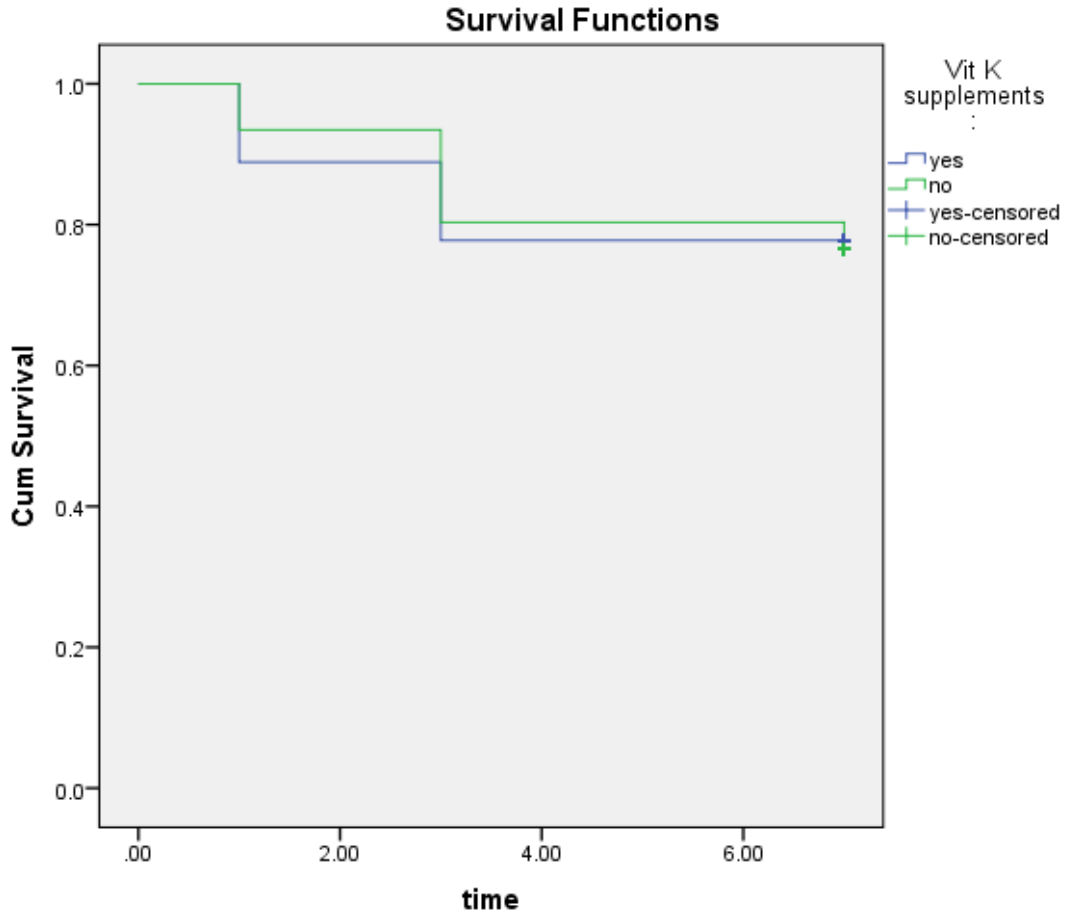


Figure 27 – Effect of Vitamin K on the Probability of DVT free survival in the MICU (p=0.99)



DISCUSSION

INCIDENCE OF DVT IN THE MEDICAL INTENSIVE CARE UNIT

In our medical intensive care unit, despite adequate thromboprophylaxis, the incidence of DVT was found to be 17.2% (12.0, 22.3) during the first seven days of ICU admission. The mean duration of ICU stay had been nearly a week in this group. However, two thirds of these DVTs were catheter related (related to and therefore provoked by the insertion of a central venous catheter or a dialysis port) and the incidence of non-catheter related DVTs was only 5.9% (2.6, 9.1), which was considered to be clinically significant. Nearly three fourths were proximal lower limb DVTs, (only a small proportion were distal lower limb DVTs in our study) while the remaining were contributed by upper limb DVTs (all jugular).

Overall, nearly half the DVTs had resolved spontaneously, over the subsequent 3 days, and nearly three fourths had resolved by a week. Less than 10% (8.6%) of these patients had been discharged with a diagnosis of DVT, after being started on oral anticoagulation therapy for the same. This contributed to 1.5% of the study population, who had developed clinically significant and proximally propagating DVTs during their hospital stay, thus, necessitating the initiation of oral anticoagulation.

The natural course of catheter related DVTs was slightly more favourable than the non catheter related ones. In the former, spontaneous resolution in 3 and 7 days from onset, had been observed in 50% and 80% respectively, while in the latter, the same had been seen in one thirds and two thirds respectively. Therefore, the catheter related ones appeared to show faster resolution.

The mean duration of hospital stay was found to be longer (with the median duration being nearly twice as long) in patients with DVT. Although, it would be premature to conclude that this

effect was solely attributable to the presence of DVTs, two reasons were initially hypothesized for this association. Firstly, the patients who had developed DVT could have had more severe illness, thereby, requiring a longer duration of hospitalization, largely owing to the overall severity of illness, which in itself could have also predisposed to the presence of DVT also. Secondly, this could be due to the presence of the DVT per se. However, there was no significant difference between the SOFA scores (which was the surrogate marker for severity of illness) of the DVT and the non DVT groups, and hence no difference in the severity of illness between the two groups, thereby implying that the presence of DVT per se is the more biologically plausible explanation for the longer duration of hospitalization.

The proportion of sudden deaths was more in the DVT group, but this observation was not statistically significant. There was no documented pulmonary embolism in our study. There was no significant difference in the secondary outcomes between the non catheter related and the catheter related DVTs. The mean duration of hospitalization (29.17 vs. 19.77) and the mean duration of hospital stay at the time of development of DVT (9.33 vs. 6.13) was found to be apparently longer in the non catheter related group, although there was no statistical significance. Therefore, in contrast to the catheter related DVTs which occurred earlier, the non catheter related DVTs had a tendency to occur with a longer period of hospital stay.

The probability of DVT free survival in the medical ICU within the first week, varied inversely with the duration of ICU stay, with the steepest drop being observed at day 3. Therefore, it was interesting to observe that while probability of acquiring a DVT increased with the duration of ICU stay, the presence of DVT, in turn, increased the duration of hospitalization.

RISK FACTORS FOR DVT IN THE MEDICAL INTENSIVE CARE UNIT

The risk factors significantly associated with the development of DVT in the MICU were determined to be elderly age (>40 yrs), presence of central venous catheters (especially femoral), administration of vasopressors and the day 3 PT/INR. However, central venous catheters were found to be independently associated with the development DVT in the medical ICU. Age and day 3 INR were also found to confer risk, but did not exhibit statistical significance. As a large number of DVTs, encountered in our study (nearly two thirds) had been catheter related, the presence of central venous catheters was thought to overshadow the other risk factors in our analysis, Therefore, risk factor analysis for the non catheter related DVTs was done, as these DVTs were considered to be unprovoked and hence the risk factors implicated in the development of the same were thought to be truly reflective of the interplay of the factors involved in the Virchow's triad.

The risk factors significantly associated with the development of non catheter related DVTs in the medical ICU included age (>40yrs), central venous catheters (especially jugular), day 3 PT and day 1 platelet counts. The occurrence of risk factors was similar to that seen with the overall DVTs. However, none of them were found to be independently associated with the development of non catheter related DVTs in the medical ICU. This was largely attributed to the small event rate (12 vs. 168). Therefore, it was seen that the presence of central venous catheters and older age were important risk factors in the medical intensive care setting for the development of DVT (irrespective of its association with a central venous catheter).

Older age (more than forty years), the presence of central venous catheters or dialysis ports and administration of vasopressors were found to reduce the probability of DVT free survival in the Medical Intensive Care Unit.

The clinical significance of the DVTs observed in our study was not known.

Only 1.5% of the patients studied (8.6% of patients who had developed DVT in the MICU) had been started on anticoagulation for DVT. It was presumed that the DVTs in the remaining patients had resolved before discharge.

The overall mortality rate in this study was 24.7, with 25.7% in the DVT group and 23.8% in the non DVT group, with an absolute risk increase of 1.9%; however this observation was not statistically significant.

Therefore, to determine the influence of deep venous thrombosis on the in-hospital mortality of patients getting admitted to the medical intensive care unit, risk factor analysis was done. The presence of DVT (overall/incident/non catheter related) did not appear to affect the in-hospital mortality of patients. The presence of DVT appeared to confer a relative risk of 1.17 (0.7, 1.95) on the in-hospital mortality, but this was not statistically significant. Larger studies are required to understand the clinical significance of these DVTs. The risk factors which were independently associated with in-hospital mortality of patients included mechanical ventilation and APTT (day 3).

REGIONAL RELEVANCE - COMPARISON WITH INDIAN DATA

A retrospective study was done in our hospital, a few years ago, to determine the incidence of DVT. This study included all hospitalized patients who had been diagnosed with DVT between 1996 and 2005. The incidence was estimated to be 17.46 per 10,000 hospital admissions, of which the large majority (93%) were lower limb DVTs (of which two thirds were proximal). However, as this was a retrospective study, details regarding the extent, adequacy and type of thromboprophylaxis was not known.(21)

Although, it was thought earlier that the risk for DVT was higher among surgical than medical patients, one of the studies from India have shown that medical patients have a higher risk of venous thromboembolism as compared to surgical patients (6.48 vs. 5.0).(32) This is largely attributable to the dynamic interplay between the three factors of the Virchow's triad, which is more commonly seen in the former group.

A study from the All Indian Institute of Medical Sciences showed that the incidence of DVT among hospitalized patients in the general medical wards and intensive care unit was 3%. This was a prospective study used the ultrasound Doppler to detect DVT, similar to our study protocol. Screening ultrasound scans were done within the first few days of admission and before discharge. All the DVTs encountered in this study were proximal lower limb DVTs and all were asymptomatic. This observation was similar to our study, wherein, most of our patients with DVT were asymptomatic (94.3%). However, in contrast to our study, none of the patients were on thromboprophylaxis; which was surprising, given the low incidence quoted by this study.(9) However, it is to note that this study was done only in patients with limited mobility.

Another study from the same institute showed that the clinical signs and symptoms of DVT were present in 25.8% of patients in the medical wards and medical intensive care units. This study

also showed that although 75% of patients had been at high risk for developing DVT at the time of admission into the medical wards or intensive care units, only 12.5% had been on thromboprophylaxis.(8) This again reflects the poor utilization of thromboprophylaxis by Indian hospitals.

A study done amongst geriatric patients admitted to the general medical wards and medical intensive care unit, in a hospital in Mumbai, showed that although 13.5% of patients had incident DVT as detected by the ultrasound Doppler, only 2.7% were clinically evident. In this study also, the thromboprophylaxis coverage had been incomplete. Amongst patients admitted to the intensive care unit, only 42% were on thromboprophylaxis. (22)

A study done in a hospital in Uttar Pradesh looked at the efficacy of thromboprophylaxis among a small group of patients admitted to the medical and surgical intensive care units. This was a randomized controlled trial, with two thirds being on thromboprophylaxis, and one thirds off the same. The overall incidence of DVT was 13.8% with the incidence of DVT amongst those on and off thromboprophylaxis being 8.3% and 25% respectively. This study shows a relative risk reduction of 66.8% in the occurrence of DVT reflecting the efficacy of thromboprophylaxis. This difference was however not statistically significant due to the small sample size studied.(51)

A prospective study from Chennai, done among patients admitted to the intensive care unit, showed that the incidence of DVT was 6.6% in the absence of thromboprophylaxis. The mean duration of stay was 4 weeks and all patients underwent screening ultrasound Doppler at 1-2 weeks of admission into the ICU. There were no pulmonary emboli encountered by this study.(52) This was surprising as the incidence rate was low despite absence of thromboprophylaxis. However, in this study, only a single screening ultrasound Doppler scan was done. Studies have shown that periodic surveillance with ultrasound screening increases the detection of DVT in the medical ICU

as most of the patients are asymptomatic. It was speculated that more frequent screening could have probably increased the yield in this study.

On comparing our study with the afore-mentioned Indian studies, the following points were evident:

1) There is no data from India on DVT exclusively in the medical intensive care unit. Two of the above studies have been done in medical wards and intensive care units, and two in medical and surgical intensive care units, and therefore, the interplay of risk factors indigenous to the medical intensive care setting may have been diluted. Therefore, they may not be truly reflective of the risk for development of DVT as imposed by the medical intensive care unit and the interventions, unique to the same.

2) Although, the current ACCP 2012 guidelines, clearly state that all critically ill patients, need to be considered at high risk for development of DVT and hence be started on some form of thromboprophylaxis; it was seen that this was not being followed by most Indian hospitals and intensive care units. Therefore, the risk for DVT for a patient admitted to the medical intensive care unit, while on thromboprophylaxis as per protocol, was still largely unknown.

3) Most of these studies have looked into the development of proximal lower limb DVTs, while ignoring the presence of upper extremity thrombi.

4) The course of the DVTs encountered in most of these studies and the therapeutic interventions have not been clearly defined. Therefore, the need for initiation of anticoagulation in these patients with ICU-acquired DVT is not known.

GLOBAL SIGNIFICANCE - COMPARISON WITH GLOBAL DATA

A group in Boston, had published their study in 1995, which bore close resemblance to our study, in terms of the study population and the methods used in the diagnosis of DVT. This was one of the few studies which had looked at the occurrence of DVT in the critically ill medical patients. The study population included patients from the medical intensive care unit, similar to our setting. The incidence of DVT was 33% (1), which was very high in contrast to the 17.2% incidence in our study. This difference could be attributed to the fact that this study was conducted at a point in time, when thromboprophylaxis had not become part of standard care in the medical intensive care setting. The thromboprophylaxis coverage in this study was 61%, as compared to our study where there was 100% coverage.

A Chinese study, done nearly a decade later, reported the incidence of DVT to be 19% in the intensive care setting in the absence of thromboprophylaxis.(33) This was close to our estimate of 17.2%, despite 100% thromboprophylaxis. However, it would be premature to conclude that thromboprophylaxis does not impact the development of DVT. In our study, the incidence of the more clinically relevant non-catheter related DVTs was only 5.9% in contrast to the former.

A study from Beijing determined the incidence of DVT at 15.1%, which was also close to our estimate of the same. However, the institution of thromboprophylaxis in this study and the extent of the same is not very clear.(35) It was seen in a study from Thailand that the incidence of DVT was 8.82% although, adherence to thromboprophylaxis was not complete in this study too.(37) A retrospective study done recently in Iran estimated the incidence of DVT to be much lower, at 5.2%. The extent of thromboprophylaxis coverage in this study is also not clear.(38)

A Canadian study in the medical and surgical intensive care unit, showed a relatively low incidence of DVT, similar to the Iranian study (5.4%), with two thirds being covered with thromboprophylaxis. However, this low number could be attributed to 2 reasons. Firstly, there was no regular surveillance for the development of DVT and secondly, ultrasound was used to diagnosed DVT only in those with a high index of clinical suspicion.(26) Our study has shown that the majority of the DVTs in the medical intensive care setting were asymptomatic; and hence screening only those symptomatic for DVT creates a large potential to miss the asymptomatic DVTs which could have occurred.

Therefore, the afore mentioned studies show that the incidence of DVT is highly variable in the medical intensive care setting, ranging from 5 to 33% across the globe. This variability is probably directly attributable to the absence of standard protocols and hence wide differences in the thromboprophylaxis administered (both extent and type) and the periodic ultrasound surveillance.

Even in the global scenario, there are only a few DVT studies which have been done in the medical intensive care unit, with patients on thromboprophylaxis.

It was seen in a study from Los Angeles, that the incidence of DVT amongst critically ill trauma patients was 13%, with adequate (98.5%) thromboprophylaxis.(53) This was also surprisingly close to our estimate, given that the study was done in a higher risk group (trauma patients). This shows that the differences which were earlier thought to exist between surgical and medical patients; and between the west and India, in the risk for development of DVT, are no longer applicable and the risks are probably similar across all hospitalized patients. A study from Massachusetts, showed that the incidence of proximal lower limb DVT was 12% with 92% thromboprophylaxis coverage.(40) The estimates from these two studies are close to our estimates.

Surprisingly, another study from the USA, showed that the incidence of DVT was 23.6% among the MICU patients with prolonged mechanical ventilation (>7days), with all of them being on thromboprophylaxis. This was quite strange as this study quotes one of the highest incidences of DVT while on thromboprophylaxis (even higher than in patients not on thromboprophylaxis).(39)

Our study showed that the incidence of DVT in the MICU was 17.2% with 100% thromboprophylaxis coverage (56% on pharmacological, 42% on mechanical and 2% on both). *The following reasons could explain the higher incidence of DVT, encountered in our study despite thromboprophylaxis, as compared with some of the above studies.*

1) Transient DVTs (Vanishing thrombi):

Although, this incidence of DVT could be considered high, while on thromboprophylaxis, it was seen that nearly three fourths of these DVTs were transient and resolved within a week (with half resolving over 3 days). Also, two thirds were catheter related and were found to have a more favourable course with faster resolution. Our frequent and regular ultrasound surveillance within the first week of ICU stay, helped us to define the natural course of the DVTs developing in the medical ICU. This reflects the subtle interplay of the pro coagulant and anti coagulant mechanisms, which is heightened in the intensive care units.

2) Catheter related thrombi:

The catheter related DVTs contributed to two thirds of the incident DVTs in the MICU. The incidence of the non catheter related DVTs was found to be 5.9%. These DVTs were thought to be more clinically significant and reflective of the true imbalances in the Virchow's triad, caused by the interventions in the intensive care setting; as the former were thought to be provoked by the presence

of a catheter which causes direct endothelial injury and thereby directly activating the procoagulant cascade.

3) Inclusion of the upper extremity thrombi:

While most of the studies cited above have described only the presence of proximal lower limb DVT, our estimates could be higher due to inclusion of the upper extremity thrombi. The occurrence of venous thrombi in both, upper and lower limbs, were thought to be more reflective of the pathophysiological mechanisms involved. As central venous catheters are being widely used in the intensive care units, which have been implicated as risk factors for the former, it was deemed prudent to include the upper limb thromboses also in our study.(54) Also, the complications of pulmonary embolism and thromboembolic pulmonary hypertension, which have been classically seen with proximal lower limb DVTs, are found to occur in patients with upper extremity thrombi as well.(5,42)

The PROTECT trial showed that despite 100% pharmacological thromboprophylaxis, the incidence of proximal lower limb DVT was 5.4% .(41) The incidence of proximal lower limb DVT in our study was 11.8%. It should also be remembered that, while all the patients in the PROTECT trial were on pharmacological thromboprophylaxis, only 58% were on the same in our study. The remaining had contraindications to pharmacological prophylaxis and therefore, had been on mechanical thromboprophylaxis. The incidence of non leg DVT was 2.2%(42) in the former, while it was 3.9% in our study. The Boston study(1) had also shown that the majority of DVTs encountered were from the proximal lower limb, and nearly two thirds were associated with the presence of a central venous catheter; which was similar to the observations in our study. Our upper extremity thrombi were contributed solely by the jugular involvement. A similar observation was also seen in

another study where the large majority of upper extremity thrombi were attributed to the internal jugular.(5)

70% of the DVTs encountered in the Boston study were detected within the first 5 days of ICU stay.(1) The Chinese study(33) showed that most of the DVTs in the intensive care setting occurred at day 3, similar to our observations. In our study, it was seen that the probability of DVT free survival in the medical intensive care unit decreased with a longer duration of MICU stay, with the steepest drop being observed at day 3 of ICU stay.

The Chinese study also showed that a large number of DVTs encountered in the medical ICU were asymptomatic, with only 27% being symptomatic.(33) This concept of asymptomatic DVTs was further established by an Indian study where all the DVTs had been asymptomatic.(9) In our study, it was seen that only 5.7% of the DVTs observed in the MICU were symptomatic.

The catheter related DVTs contributed to 40.5% of the incident proximal lower limb DVTs and 51% of the non leg DVT in the PROTECT trial.(41,42) The frequency of catheter related thrombi were higher in our study, with them contributing 64.7% of the proximal lower limb DVTs and 80% of the upper extremity DVTs.

In the Boston study, it was seen that 21% of patients with DVT required therapeutic intervention (in the form of insertion of IVC filters in 9% and initiation of oral anticoagulation in 12%) (1), in contrast to our study, where only 8.5% (1.5% of the entire study population) required therapy in the form of initiation of oral anticoagulation. In contrast, the Chinese study had shown that 40% of patients with DVT required initiation of anticoagulation therapy.(33)

It was seen in the Chinese study(33) that the mortality in the DVT group and the non DVT group was 33 vs. 28% as compared to our study where the same was 25.7% vs. 23.8%. This difference was smaller in our study and hence not statistically significant. A few studies have shown that the

presence of DVT increases the duration of ICU stay and hospitalization.(41,42,53) Similar trends were also observed in our study. The difference in the length of hospital stay was statistically significant with the duration of hospitalization in the DVT group being nearly 10 days more than that in the non DVT group.

Clinically important DVTs were defined as those that were likely cause short term or long term morbidity or mortality, in contrast to those that were devoid of clinically significant consequences. A survey done among intensivists, revealed three patient factors and three sonological factors which, when present, increased the likelihood of a clinically important DVT. The former were leg symptoms, clinical suspicion of pulmonary embolism and poor cardiopulmonary reserve as a result of co-morbid conditions. The latter included proximal site, large size and total occlusion of the venous lumen by the thrombus.(55) In our study, the frequency of patient factors and sonological factors were as follows:

Patient Factors:

1) Leg Symptoms: They were seen in 10 patients in the overall study population, of which only 2 developed proximal lower limb DVT. Although the incidence of symptomatic DVT amongst those with leg symptoms was 20%, the same among the entire study population, was very low, at nearly 1%. Therefore, only 1% of patients getting admitted to the medical ICU developed symptomatic DVT.

2) Clinical suspicion of pulmonary embolism: Although there were no cases of confirmed pulmonary embolism in our study, there were 9 sudden deaths, one third of which happened in the DVT group. Among these sudden deaths, there was a clinical suspicion of pulmonary embolism in one patient (1/203=0.05%), who had femoral and jugular thromboses.

3) Poor cardiopulmonary reserve: As our study was conducted in a medical intensive care unit, most of the patients had poor cardiopulmonary reserve, given the overall requirement of mechanical ventilation and vasopressors being 75% and 54% respectively.

Sonological Factors:

1) Proximal site : This was seen among those with femoral and jugular thrombi. The incidence of proximal deep venous thrombosis was 16.7% in our medical ICU.

2) Totally occlusive thrombi: The incidence of totally occlusive thrombi or DVTs causing complete thrombosis was 4.9% in our medical ICU.

Therefore, considering the above attributes, although the incidence of DVT in MICU was 17.2% in our study (with that of non catheter related DVTs being 5.9%), not all satisfied the above criteria for clinically important DVT. Also, the incidence of DVTs requiring initiation of oral anticoagulation at discharge was only 1.5%. *This implies a favourable course with standard thromboprophylaxis, with most of the ICU acquired DVTs resolving spontaneously, especially the catheter related ones.*

COMPARISON OF RISK FACTORS FOR DEVELOPMENT OF DVT IN MICU

A retrospective study done in our hospital amongst all hospitalized patients with a diagnosis of DVT, determined malignancy and surgery to be the two most important risk factors. While this is applicable to most surgical patients, they cannot be directly applied to medically ill patients, especially in the criticare units, as the risk factors endogenous to the intensive care setting are unique.(21)

A study done in Mumbai, in the medical and surgical intensive care unit showed that the risk factors implicated in the development of DVT in the critically ill were older age, prolonged bed rest (among medically ill patients), surgery and central venous catheters (among surgical patients). (32) These observations were similar to those made in our study, wherein, the important risk factors recognized in the development of DVT in the medical ICU, irrespective of whether they are catheter associated or not, included central venous catheters, older age, vasopressors and day 3 INR, of which only the presence of central venous catheter was independently associated.

In the Boston and the Chinese studies (with inadequate thromboprophylaxis), the risk factors for development of DVT in the medical intensive care setting were studied. None of the factors traditionally implicated in the development of DVT in the intensive care setting was identified by these studies. This was probably attributable to their small study population.(1,33)

The Beijing study, which was largely done in the emergency and the respiratory intensive care setting had identified renal failure, history of surgery and d-dimer as risk factors for development of DVT in the ICU.(35)

The Canadian study done in the medical and surgical intensive care setting had identified femoral venous catheters, mechanical ventilation, sedatives and paralytic agents as risk factors, similar to our study which had primarily picked up factors endogenous to the intensive care unit, in the form

of central venous catheters and vasopressors as ones conferring maximum risk of DVT to these patients. Only thromboprophylaxis and warfarin were found to be protective against the development of DVT in this study. However, this study included DVTs occurring even prior to the admission in the intensive care unit and hence the risk factors may not be strictly indigenous to the intensive care setting.(26)

The Thailand study done exclusively in patients admitted to the medical intensive care unit identified the presence of older age, central venous catheters, female gender and renal replacement therapy to be the risk factors associated with the development of DVT. This was similar to the results of our study which had also identified central venous catheters to be independently associated with DVT development in the medical ICU.(37)

A study done in Boston, showed that the strongest predictor of upper extremity catheter related DVT was the presence of a central venous catheter, while the predictors of non catheter associated DVTs included longer hospitalization, smoking and lean body habitus.(54)

Therefore, the common risk factors which echoed through most of the afore mentioned studies, thereby implying its strong association with the development of DVT in the MICU include the presence of central venous catheters and older age of the patient. The identification of these risk factors has several implications in the medical intensive care unit. As the presence of central venous catheters emerged as the sole independent risk factor for the development of DVT in the intensive care setting, they should be appropriately used with discretion. The duration of the central venous catheters was also found to influence the development of DVT. Therefore, the removal of central venous catheters needs to be considered at the earliest in each patient, with regular assessment for DVT. Also, special attention towards the elderly is warranted with periodic ultrasound surveillance for the presence of DVT.

LIMITATIONS

This study was done as a prospective cohort study in the Medical Intensive Care Unit over a period of 10 months (June 2013 to April 2014).

The recruitment of patients was planned as a consecutive sampling. Due to practical constraints, there were small lapses, despite which, consecutive sampling was attempted to the best possible extent.

The study protocol included three consecutive ultrasound screening scans on the days 1, 3 and 7 from the time of admission into the MICU. Although, repeat screening ultrasound scans at regular intervals, may have been ideal till the time of discharge; due to practical feasibility constraints, this could not be done. Although it was seen that nearly half of the DVTs had resolved over the subsequent 3 days, and three fourths over a week; details regarding the time to resolution in the remaining patients could not be ascertained due to the above constraints.

This study was restricted to the patients belonging to any of the five medical units in the hospital. There were patients from other medical specialties (like hematology, rheumatology, gastroenterology, cardiology, nephrology, neurology, medical oncology and endocrinology) who had got admitted to the MICU. They had not been considered for inclusion into the study as per protocol. The prevalence of certain risk factors for the development of DVT, which include, malignancies, thrombophilias, autoimmune diseases, and endovascular procedures & devices, may have been higher in those patients from the afore mentioned specialties, especially hematology, medical oncology and rheumatology. Exclusion of these patients creates a lacuna in our understanding of DVTs and the adequacy of thromboprophylaxis in this high risk group.

The management of the DVTs encountered in this study was done according to the discretion of the treating physician. As a result, follow-up formal Doppler scans to look for progression or resolution of DVTs were not uniformly done in all patients with DVT. Initiation of oral anticoagulation was done in 13.6% (n=3/22) of patients with incident DVT who were discharged alive. These patients had become symptomatic during the later part of their hospital stay and the formal Doppler screening had revealed occlusive thrombus with proximal extension, which prompted initiation of anticoagulation. The resolution of DVT in the remaining patients was presumed at discharge from the hospital. Although these patients had been monitored in the ward for clinical features suggestive of DVT or its proximal propagation, most of the DVTs detected in the MICU were asymptomatic, implying the need for periodic surveillance with Doppler ultrasound in these patients; which was not done.

Although the duration of central venous catheters was known in all the patients, a repeat Doppler scan following the removal of central venous catheters in patients with catheter related DVT would have been ideal, which was not done due to practical difficulties and feasibility constraints . A follow up scan following the removal of catheter would have not only ascertained the resolution, but would have also been helpful in determining the time to resolution. Determination of the time to resolution would have been useful while approaching the management of catheter related DVTs, as persistence beyond this time, would necessitate initiation of anticoagulation.

MERITS

Our study is one of the few prospective studies in the country to describe deep venous thrombosis. It is the first study in India, to describe the occurrence of DVT exclusively in the medical intensive care unit. It is also the first in India to study patients while on thromboprophylaxis (100% coverage). The need for assessment of DVT among a high risk group (critically ill hospitalized medical patients) in a standard protocolized environment (while on thromboprophylaxis) was the driving force behind this study.

A uniform protocol (Appendix 1) for thromboprophylaxis was followed by all doctors in the medical intensive care unit, as a result of which all the patients studied were on standard thromboprophylaxis (pharmacological/mechanical/both). Therefore, the results are applicable to patients on thromboprophylaxis.

Regular screening ultrasound scans done at strategic points during the first week of admission into the MICU (which had been earlier identified by studies to be the high risk period for developing DVT) helped to detect several asymptomatic DVTs. The day 1 scan helped to exclude the DVTs at admission thereby, helping us to calculate the exact incidence of DVT after arrival into the MICU. Day 3 and day 7 scans were planned as studies had previously shown that the maximum incidence of DVT in the MICU was after 48 hrs of ICU stay and after a week. This was helpful as our study helped to delineate the timeframe for the development of DVTs and their course in the medical intensive care setting.

As our study was done exclusively among patients from a medical intensive care unit; this was a more homogenous population being studied, the results of which will be applicable to patients in other medical ICUs. As this study was done in a hospital where the intensive care units are well integrated with the medical wards, the follow up was complete.

CONCLUSION

Venous thromboembolism is one of the most common preventable causes of death in hospitals. Early recognition and appropriate management of deep venous thrombosis helps to save human lives and hospital resources. The risks for development of the same have been found to be similar across the world. Although, this entity was initially described among surgical patients, recent studies have shown that the risks are similar among medical patients, but arising from interplay of factors different from those in the former. Studies have shown that despite thromboprophylaxis being the standard of care in intensive care settings, it is largely underutilized in India.

Our study showed that the incidence of DVT among critically ill patients in the medical intensive care unit was 17.2% on standard thromboprophylaxis. Hence , there needs to be a low threshold for suspicion of DVT among the patients admitted to the medical intensive care unit.

The incidence of non catheter related DVT was 5.9%. Only 13.6% of those with DVTs who were discharged, required to be started on oral anticoagulation therapy. Majority of the DVTs, especially the catheter related ones, had a favourable course. This could be attributed to meticulous thromboprophylaxis and timely removal of central venous catheters. Although, a large number of DVTs acquired in the medical intensive care unit, tend to resolve spontaneously and hence, have no effect on mortality, they seemed to increase morbidity. This was reflected by the observation that *the presence of DVT appeared to increase the median duration of hospital stay by 10 days, thereby draining the financial and health care resources.*

The presence of central venous catheters seemed to independently influence the development of DVT in the medical intensive care setting. This risk was higher in the older patients. *Hence, periodic Doppler surveillance and appropriate use of central venous catheters and their timely removal would be helpful in the management of the DVTs in the medical intensive care unit.*

APPENDICES

Appendix 1 - BIBLIOGRAPHY

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Appendix 2 – PROTOCOL FOR THROMBOPROPHYLAXIS

All patients admitted in MICU/MHDU, are to be considered for thromboprophylaxis from day of admission into ICU/HDU. (50,56)

Guidelines to be followed:

All patients are to be on unfractionated heparin by default, unless contraindicated, at a dose of Inj. Heparin 5000U S/C BD

As an alternative, the patients may also be started on one of the following, instead of unfractionated heparin, depending upon the physician's choice

Inj. Dalteparin 5000U S/C OD (or)

Inj. Enoxaparin (Clexane) 60mg S/C OD (or)

Inj. Fondaparinaux 2.5mg S/C OD

In the case of the following situations where anticoagulation is not advisable, the patient is to be on TED stockings.

Severe thrombocytopenia (<50000)

Deranged bleeding parameters (INR>1.5 or APTT >6s over the control)

Active bleeding (from any site) or active gastroduodenal ulcer

Recent stroke or History of bleeding in the past 3 mths

Hypersensitivity to any of the above drugs

Appendix 3 – DEFINITIONS

Outcomes:

DVT:

Patients with any one or both of the following features on a screening ultrasound on D1/D3/D7 at any site and at one or more sites examined:

Lack of compressibility on ultrasound

Visualization of thrombus

Death:

a. ICU death: Mortality during the first seven days of admission to MICU/MHDU. (all causes / pulmonary embolism / sudden death)
b. Hospital death: Mortality before discharge of the patient from the hospital. (all causes / pulmonary embolism / sudden death)

Pulmonary embolism:

A PE was categorized as definite when confirmed by pulmonary angiogram, computed tomographic scan, magnetic resonance image, or pathologic examination of thrombus removed at surgery or autopsy(21) (or) in a patient with ECG (sinus tachycardia/S1Q3T3/T inversion in V1-V4) findings plus ECHO (RA/RV dilatation/RV hypokinesia) findings suggestive of pulmonary embolism with high clinical probability of pulmonary embolism.(10)

Sudden death:

Death in an otherwise hemodynamically and neurophysiologically stable patient, for which cause could not be attributed at the time of death.

Discharge:

Patients who have been discharged from hospital within completion of a week from the time of admission into the ICU/HDU and therefore the remaining data to be collected in those patients will be considered as missing data for all practical purposes.

Exposures:

Past history of

Surgery(43) – Recent surgery within the past 4 weeks, lasting for >1hr,

requiring atleast 3 days of post op hospitalization

Major abdominal surgery

Major orthopaedic surgery

Neurosurgery

Surgery for polytrauma

Trauma(43) – Recent major trauma within the past 4 weeks,

Major trauma – fracture / crush injury

Especially involving the extremities,

requiring atleast 3 days of hospitalization as part of its treatment

Previous DVT/Pulmonary embolism(43) – previous diagnosis of a

pulmonary embolus or deep venous thrombus,

based on objective methods (imaging)

irrespective of the time of diagnosis

DVT was categorized as definite when confirmed by venogram, computed tomographic scan, magnetic resonance image, or pathologic examination of thrombus removed at surgery or autopsy. A PE was categorized as definite when confirmed by pulmonary angiogram, computed tomographic scan, magnetic resonance image, or pathologic examination of thrombus removed at surgery or autopsy.(21)

Intake of OCPs/HRT(57,58) – for more than 3 months

(concurrently at the time of admission or discontinued for not more than 1 week prior to admission)

Hospitalization(59) – for more than 2 days (for any reason)

Congestive Cardiac Failure(60) – Left Ventricular systolic dysfunction –

Presence of both clinical features suggestive of cardiac failure

(orthopnea, bibasal crepitations, NYHA-Class III-IV (61)) plus

Ejection fraction of =< 45% on ECHO

Permanent pacemaker inserted (62)

Chronic Kidney Disease(63) – patients requiring dialysis or

Those diagnosed with nephritic syndrome

Chronic Liver Disease(64) – patients with clinical features and

imaging suggestive of liver cirrhosis during

the study or prior to it.

COPD(65) - Spirometric evidence as suggested by GOLD criteria.

FeV1/FVC<70% and

post bronchodilator FeV1<805 of the predicted value

Clinical and radiological features will be taken in to account in case of non availability of spirometry.

Malignancy - Patients with any of these malignancies

including breast, colorectal and lung, cancers of the pancreas,

ovary and brain or on anti neoplastic drugs for the same(66).

(Active malignancy (or) currently on chemotherapy or palliation

For the same or (or) completed treatment

in the past 6 mths.)(43)

Varicose Veins - All patients with varicose veins according to

international classification of diseases code: 183.9

Hypertension(12) – Blood pressure of > 140/90 as an

average of 2 or more seated readings during

each of 2 or more out patient visits

Diabetes Mellitus(12) –

Clinical features of diabetes plus random plasma

glucose levels > 200mg% (or)

Fasting plasma glucose levels > 126mg% (or)

2hrs after oral glucose tolerance test,

plasma glucose levels > 200mg% (or)

HbA1C levels > 6.5%

Thrombophilias(12) – congenital or acquired states of hypercoagulability

Predictors:

Age

Sex

Body Mass Index

Duration of hospital stay

Duration of ICU stay

Mechanical ventilation

Central venous catheters / Peripherally inserted central catheters

Use of sedatives/muscle relaxants/vasopressors

Dialysis

Transfusions

Effect Modifiers: (with respect to thromboprophylaxis)

Smoking & Alcohol - Patients satisfying DSM IV TR criteria for alcohol and nicotine dependence syndrome.

Antiplatelets – Intake during the previous 1 week or concurrently(50)

Vitamin K supplements during the previous 1 week or concurrently(50)

Appendix 4 – DATA ABSTRACTION FORM (CLINICAL RESEARCH FORM)

Serial No:	**Hosp. No:**

DRIVE STUDY – DETERMINATION OF INCIDENCE AND RISK FACTORS OF DEEP VENOUS THROMBOSIS IN THE MEDICAL INTENSIVE CARE UNIT
DATA ABSTRACTION FORM

Name: **Age:** **Sex: Male / Female**

Address: **Weight(estim):**

Contact number: **Height:**

PRIMARY ADMISSION / RE-ADMISSION

Admission source: Same hospital ED / Same hospital ward / Inter-hospital

Date of hospital admission: **Admission diagnosis:**

Date of ICU admission:

Discharge date: **Discharge diagnosis:**

Risk factors/Co-morbidities: (Circle features present at admission)

Past History	Present History	
Surgery/Trauma(<4weeks)	Pacemaker Insertion	Malignancy
Hospitalization>3days	Congestive cardiac Failure	Hypercoagulable states
Previous DVT/ Pul.embolism	Chronic liver failure	Pregnancy/Post partum
Central lines / Dialysis ports	Chronic renal failure	Immobilization (stroke/paresis)
OCP intake(<4weeks)/HRT	Smoking	Alcohol intake
NSAIDs use	Aspirin/Clopidogrel	Vit K supplements
Rheumatic/autoimmune d/s		
Other Drugs(list)		

Others (list)	

SOFA	0	1	2	3	4
Respiratory P/F	> 400	< 400	< 300	< 200	< 100
Platelets	> 150	< 150	< 100	< 50	< 20
Vasoactive	Nil	MAP < 70	Dopa < 5	Dopa > 5 or Adr/NA <0.1	Dopa >15 or Adr/Na >0.1
GCS	15	13-14	10-12	6-9	< 6
Bilirubin	< 1.2	1.2 – 1.9	2.0 - 5.9	6.0 -11.9	> 12
Renal	< 1.2	1.2 – 1.9	2.0 – 3.4	3.5-4.9 or UOP < 500 ml	> 5.0 or UOP < 200 ml

SOFA Scoring at presentation =

Local features: erythema / warmth / swelling / tenderness / none

Treatment details

	Site/Comments	From(date)	To(date)	Duration
Central venous lines				
Peripherally inserted central lines				
Dialysis Ports				
Mechanical Ventilation				
Sedatives				
Muscle Relaxants				
Vaopressors				
Transfusions				

Diagnosis:

SITES	DAY # 1 ----/----/----	DAY # 3 ----/----/----	DAY # 7 ----/----/----
Right jugular			
Left jugular			
Right axillary			
Left axillary			
Right femoral			
Left femoral			
Right Popliteal			
Left Popliteal			

C- Vein compressible

N-Vein not compressible

P-Vein partially compressible

NV-Vein not visualized

T-Thrombus visualized

Most recent value on /before	D1 ___/___/___	D3 ___/___/___	D7 ___/___/___
PT/INR			
APTT			
platelets			

Thromboprophylaxis:

None / Pharmacological / Mechanical(TEDS) / Both

If Pharmacological → LMWH / UFH / Fondaparinaux

If LMWH → Enoxaparin / Dalteparin

Dosage:

Outcome:

DVT Present: yes / no

D1 DVT: yes / no

Day of development of DVT:

From the day of hospital admission:

From the day of ICU/HDU admission:

Site of DVT : jugular / axillary / femoral / popliteal

Side of DVT: right / left

Duration of ICU stay (days):

Duration of hospital stay (days):

ICU outcome: Dead / Alive / Discharged at request/ PVS

Hospital outcome: Dead / Alive / Discharged at request / PVS

Probable cause (s) of death: sudden death / confirmed pulmonary embolism / other causes

Appendix 5 – INFORMED CONSENT FORM

I.Information sheet

Introduction: I($) am a post graduate student under the department of general medicine, doing research on deep venous thrombosis in critically ill patients admitted in medical intensive care unit & high dependency unit. I assure you(#) that every small detail regarding your participation in this study will be explained patiently to you in your own regional language; and consent may be given only if you are fully convinced of your role in the study .

Purpose of the research: A "thrombus" is a clot in the blood vessel which usually occurs due to three factors – alterations in flow of blood, increased tendency of the blood to clot, and injury to the blood vessel wall. Deep venous thrombus refers to a clot in the deep veins of the body. It is of concern because it can lead to pulmonary embolism(clot in the pulmonary vessels) and inturn death, if not identified and treated. Deep venous thrombosis is a common problem in hospitalized patients, especially in patients of intensive care units, for which reason, there is already a pre-existing guidelines for preventing deep venous thrombosis are in place. Numerous studies pointing towards the occurrence of deep venous thrombosis in intensive care units despite measures to prevent the same, and limited studies on deep venous thrombosis in an Indian demographic, led us thinking on the lines of this topic, which necessitated a detailed evaluation and therefore shaping into this research paper.

Participant selection: You are being requested to participate/allow your relative to participate in this study as you/he/she have/has been admitted in the *MICU/MHDU. The expected duration of the requested participation in this study would be 7 days from the time of admission into the intensive care unit , i.e., from the time of entering the study.

Voluntary participation: Your participation in this research is entirely voluntary. It is your choice whether to participate or not. Whether you choose to participate or not, the management and standard of care will remain the same. If you choose not to participate in this research project, you will still continue to receive the same standards of treatment. You may change your mind later and stop participating even if you agreed earlier.

Information on the research-Procedures & Protocol : All patients admitted in the *MICU & MHDU will be started on measures which prevent clot formation in blood, from the day of admission as per the routine standard guidelines (already being implemented here). Ultrasound screening for **DVT is one of the bedside investigatory tools that is used frequently in *MICU/MHDU to pick up **DVT in patients with a high degree of clinical suspicion, as it is often seen in this setting. In this study, every patient will be screened by self (or a coinvestigator) by ultrasound for **DVT in a methodical manner, through three sequential scans over a period of one week. In addition, information regarding the patient's past history, current clinical presentation, treatment details, course in *MICU/MHDU and outcome will be collected purely for research purposes. In the event of the patient being positive for **DVT during one of the tests, the relatives and the concerned unit will be informed and treatment for the same will be commenced immediately after discussion with the parent unit and the relatives. This study will have no bearing on the outcome of the patient.

Appropriate Alternate Procedures: Bedside Compression ultrasound is an extremely safe, non invasive diagnostic tool used routinely for diagnosis of **DVT in *MICU/MHDU. Alternative procedures for **DVT include invasive procedures like venogram and more time consuming procedures like whole leg duplex ultrasonography.

Risks: This study has no risks; however the inherent risks arising from hospitalization,*MICU/MHDU stay, **DVT or its sequele will exist independent of the study.

Benefits: This study tries to elevate the standards of care already being offered to patients by offering more efficient ways than routine, of diagnosing **DVT by frequent ultrasound scans, and thereby starting early diagnosis and treatment of the same to prevent its sequele.

Reimbursements: You will not be charged the cost of the sequential ultrasound scans which are done as a part of the study. There are no other incentives. The patient will not be paid for his/her participation in the study.

Confidentiality: Your name will not be mentioned anywhere neither the data sheet nor the final published study. Your data will bear a study number and the number will be used till analysis.

Sharing of the result: The result of this research is a property of Christian Medical College, Vellore; and I am entitled to publish it in a journal or present it in a conference. The participant will have no claim towards the same.

Right to Refuse or Withdraw: You do not have to take part in this research if you do not wish to do so. You may also withdraw participating in the research after giving the consent. It is your choice and all of your rights will be respected.

II.Certificate of Consent

Study Title: Detrmination of Incidence and Risk Factors For Deep Venous Thrombosis in the Medical Intensive Care Unit

Subject's Name: _____

Date of Birth / Age:_____

Please tick the boxes:

(i) I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions. [ ]

(ii) I understand that my participation in the study is voluntary and that I am

free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. [ ]

(iii) I understand that the Sponsor of the clinical trial, others working on the Sponsor's behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published. [ ]

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s) [ ]

(v) I agree to take part in the above study. [ ]

Signature (or Thumb impression) of the Subject/Legally Acceptable

Representative:_____

Date: _____/_____/_____

Signatory's Name: _____

Signature of the Investigator: _____

Date: _____/_____/_____

Study Investigator's Name: _____

Signature of the Witness: _____

Date:_____/_____/_____

Name of the Witness: _____

Appendix 6 – GLOSSARY

DVT – Deep Vein Thrombosis

VTE – Venous Thromboembolism

PE – Pulmonary Embolism

MICU – Medical Intensive Care Unit

ICU – Intensive Care Unit

MHDU – Medical High Dependency Unit

HDU – High Dependency Unit

CMC – Christian Medical College

SD – Standard Deviation

IQR – Inter quartile Range

PT – Prothrombin Time

INR – International Normalized Ratio

APTT – Activated Partial Thromboplastin Time

DAMA – Discharge Against Medical Advice

SOFA – Sequential Organ Failure Assessment score

SPSS – Statistical Package for Social Sciences